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REVIEW ARTICLE

The role of Human Papillomavirus and Surrogate Immune Markers in Urinary Bladder Cancer in Mansoura Urology and Nephrology Centre

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ABSTRACT

Bladder cancer ranks 13th globally in terms of cancer-related deaths and is the 10th most prevalent type of cancer overall. Smoking and urinary tract infections, such as schistosomiasis, are the most reported risk factors for bladder cancer. An association between infection either bacterial or viral with cancer was reported. Human papillomavirus (HPV), Herpes simplex virus, BK virus, Bovine leukemia virus and Human immunodeficiency virus are linked with cancer development. Viruses cause about 15–20% of all types of cancers, but 10 percent are due to HPV. HPV, is DNA virus, infects the cutaneous or mucosal epithelium and belongs to papillomaviruses family. Immune. Studies have shown that immune-related markers play an important role in the diagnosis, prognosis assessment and treatment of bladder cancer. In addition, the detection of immune-related markers can also be used to evaluate the efficacy of immunotherapy and predict the treatment response of patients. HNPs 1–3 are subtypes of α-defensins, proteins that aid in the recruitment of leukocytes and might contribute to metastasis.

INTRODUCTION

Bladder cancer ranks 13th globally in terms of cancer-related deaths and is the 10th most prevalent type of cancer overall, according to the Global Cancer Observatory [1].

Urinary bladder cancer is an extremely diverse neoplasm, with around ninety percent of patients with this cancer diagnosed with urothelial carcinoma, while the remainder have squamous cell carcinoma, adenocarcinoma, or neuroendocrine tumor[2]. Hematogenous spread to many organs(adrenal glands, liver, bones, and lungs often occurs and associated with bad outcome [3].

Environmental exposure and genetic background are two risk factors for cancer development that have been studied. The primary risk factors for bladder cancer are urinary tract infections (bacterial or virus), smoking, and schistosomiasis [4].

An association between infection either bacterial or viral with cancer was reported. HPV, Herpes simplex virus, BK virus, Bovine leukemia virus and Human immunodeficiency virus are linked with cancer development. Viruses cause about 15–20% of all types of cancers, but 10 percent are due to HPV [5].

Human Papillomavirus Virus

A member of the papillomavirus family, a DNA virus that infects the mucosal or cutaneous epithelium. The icosahedral capsid that encloses the viral genome, which is roughly 8,000 base pairs long and 52–55 nm in diameter, is the characteristic structure of HPV[6].

Classification and types

Five families of HPVs were identified: α, ß, γ, μ, and v. In immunocompetent people, ß, γ infection s only result in asymptomatic infections, whereas the α genus genotypes have been linked to malignancy [7].

Of the 448 HPV genotypes that have been identified, the majority do not cause cancer [8]. Currently, only 12 types (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, and 59) are categorized as carcinogenic genotypes [9].

However, high-risk HPV types account for around 10% of cancers worldwide, including 90% of cervical cancers, most anal cancers, and some vulvar, vaginal, and penile cancers [10].

HPV and Cancer

HPV is an unencapsulated double-stranded DNA virus. Seven to nine open reading frames (ORFs) on the same strand make up its genome. The ORF is composed of three functional components: the long control region (LCR), which is primarily non-coding and necessary for transcription and replication, the upstream regulatory region (URR) or noncoding region (NCR), and the early (E) region, which encodes proteins (E1–E7) required for viral replication and the late (L) region, which encodes structural proteins (L1–L2) required for virion assembly [11].

Protein-coding genes and a noncoding regulatory long control region make up the HPV genome. The main viral oncoproteins in the coding area are E6 and E7, which have a significant impact on apoptosis, tumor suppressor pathways, telomere maintenance, cell cycle regulation, and genomic stability [11].

These consequences cause cancer to start and spread. E6 and E7 protein expression occurs after HPV infection, which causes viral DNA to integrate into the host genome. Moreover, E6 promotes the tumor suppressor protein (p53) destruction, while E7 binds to retinoblastoma protein (pRB), facilitating replication of HPV and encouraging cancerous changes[12].

HPV-induced carcinogenesis throug integration of viral DNA int the host genome, inflammation, and release of inflammatory mediators. This results in increased DNA damage and promotes cancer progression, genomic instability [13].

Studies reveal that inflammation leads to oxidative stress, DNA rupture, and HPV integration by increasing reactive oxygen species (ROS) and reactive nitrogen species (RNS), promoting carcinogenesis during viral infections [14].

Chronic inflammation increases DNA mutations and promotes proliferation, with cancer stem cells linked to infection and inflammation. More studies needed to apply this model to bladder neoplasms [15].

The majority of HPV-positive patients have high-grade, stage and decreased survival or a higher recurrence rate following transurethral resection [16].

Lab diagnosis and screening

At age 21, women should have Pap tests every 3 years, as mentioned in the guidelines of the American Society for Colposcopy and Cervical Pathology and the United States Preventative Services Task Force (USPSTF). Women over 30 who want to be screened by Pap testing every 3 years, HPV/Pap cotest every 5 years, or HPV testing only every 5 years [17]

As of 2021, the WHO advises all women to be screened for HPV using only HPV DNA testing, not by inspection with acetic acid (VIA) or cytology, beginning at age 30 and continuing every 5 to 10 years following two negative screening tests [18]

At present Centers for Disease Control and Prevention (CDC) does not suggest testing for HPV infection in men except in males with anal intercourse or who are HIV-positive may be offered anal Pap testing.[19].

Screening of HPV is frequently done for cervical and anal cancers and less in oropharyngeal cancers. Screening with ctHPVDNA, a plasma-circulating HPV marker, is one possible remedy for this [20].

HPV cannot be detected using conventional viral diagnostic techniques including electron microscopy, cell culture, and specific immunological techniques. It is not possible to cultivate HPV in cell cultures. Colposcopy and acetic acid testing, biopsies, DNA tests and Pap smears are crucial techniques for diagnosing HPV infection[21].

Pap smear or Pap test

Papanicolaou and Traut were the first to describe this screening test. In addition to premalignant and malignant alterations, viral infections such as herpes and HPV infections can be identified. A positive test necessitates additional confirmatory procedures such cervical biopsies, coloscopies, and DNA tests like polymerase chain reaction (PCR). [22].

Acetic acid test and colposcopy

Using a low-powered microscope called a colposcope, specially trained professionals perform colposcopy as an outpatient treatment. Applying an acetic acid solution to the cervix, vagina, and sometimes the vulva. Any lesions suspected of being neoplasia are then biopsied [21].

Biopsy

Biopsy from the abnormal areas is taken by colposcopy. Therapy is advised if the biopsy results reveal malignancy or dysplasia. There are three levels of dysplasia: mild, moderate, and severe. When high-grade abnormalities are revealed by colposcopic examination, excisional biopsy is advised. [21].

Molecular techniques for detecting HPV

Since HPV is not culturable, several methods were developed depend on molecular techniques for its detection. Nucleic probe technique is the foundation of the preferred tests for identifying HPV in clinical specimens [23]. Currently, many techniques as nucleic-acid amplification, signal-amplification assays and nucleic acid-hybridization assays are available [24].

HPV-DNA can also be detected using real-time PCR. Fluorescent probes and type-specific PCR primers can be used together for real-time detection. Although they have also been utilized in real-time PCR, broad-spectrum PCR primers are more difficult to quantify than type-specific primer systems but It can be technically challenging to use multiplex many type-specific primers in a single reaction. Because different HPV genotypes have different sequences, a combination of probes is required for the genotyping of PCR results from broad-spectrum PCR and standardization is challenging because each of these will have unique hybridization characteristics. [25].

Dot blot and Southern blot were two of the first direct probe hybridization techniques used for HPV detection. They required a lot of DNA in clinical samples, were time-consuming and labor-intensive, had low sensitivity[24].

Treatment

Till now for the human papillomavirus infection, there are no well-established therapies available. The diseases and symptoms brought on by an HPV infection, including cancer or warts, are the focus of the various treatments. Topical medications and manual removal or destruction are two methods of treating

genital warts. Among the topical treatments are isotretinoin, imiquimod, podophyllotoxin, and sinecatechins; imiquimod and podophyllotoxin are the most often utilized. Physical removal and destruction techniques include simple surgical excision, liquid nitrogen ablation, electrocauterization, and photodynamic therapy [26].

Cross-sectional imaging and pathology were added to the staging system by the International Federation of Gynecology and Obstetrics called FIGO in 2018. Simple hysterectomy or conization may be used to treat earlier stages, but hysterectomy, radiation, and/or chemotherapy may be necessary for later stages[27].

Historically, cisplatin-based chemotherapy was proven to be more effective when combined with other therapies such topotecan, paclitaxel, or 5-fluorouracil, or bleomycin as monotherapy may acquire resistance. Radiotherapy is often required with the combined chemotherapy in locally advanced cervical cancer [28].

Treatments of cervical cancer or anal cancer rely on staging. Small lesions can be excised locally, and they frequently don't need additional care. Before being removed, patients with more severe disease need to be treated, usually with chemotherapy and radiation. Local excision is the most often employed multimodal strategy, which is followed by radiation, mitomycin, and 5-fluorouracil. A cisplatin-based treatment must be added if the cancer has spread[29].

Treatment for HPV-related oropharyngeal cancer is similar to that for other HPV-related malignancies. The initial course of treatment is usually excision, which can be accomplished open or with less-invasive approaches including robotic and laser surgery. After excision, radiation therapy combined with chemotherapy based on cisplatin is the standard of care[30].

HPV Vaccines and its efficacy

In 2006, the HPV vaccination received its initial approval for use in the US. Bivalent, quadrivalent, and nonavalent vaccinations are the three main categories that are currently on the market. The most recent vaccination is the nonavalent, or 9-valent, vaccine sold under the Merck & Company brand name Gardasil®. It targets HPV 6, 11, 16, 18, 31, 33, 45, 52, and 58. The bivalent vaccine targets HPV 16 and 18. The quadrivalent vaccine targets HPV 6, 11, 16, and 18. [31].

The HPV vaccine is a non-infectious recombinant vaccine made from purified L1 protein particles that resemble viruses and are found in all related HPV types. In more than 98% of cases, an antibody response is anticipated one month after the vaccination series is finished. There is no known minimum protective antibody titer level[31].

Additionally, the vaccine enhances B cell immunity by altering the blood's antibody composition. Natural HPV infection results in the formation of non-neutralizing antibodies [32].

According to the CDC, the HPV vaccine offers sustained immunity against infection for a minimum of 12 years [17].

The ability of the HPV vaccine to prevent both high-risk and low-risk HPV infections and illnesses can be used to evaluate its effectiveness. Both the number of genital warts (OR = 0.36, 95% CI 0.26–0.51) and the risk of getting warts (OR = 0.03, 95% CI 0.01–0.09) were significantly reduced by the quadrivalent vaccine[33].

Children aged 11- and 12-year-old should take two doses of the HPV vaccine 6 to 12 months between them. Those between the ages of 15 and 26 who have never received an HPV vaccination should get three doses. Nevertheless, depending on factors like early sexual activity or decreased immunity state, the CDC advises vaccination as early as age 9 and catch-up vaccination up to age 45 [31].

According to the WHO, women over 21 should have two doses spaced six months apart, whereas girls aged 9 to 14 and women aged 15 to 20 should receive one or two doses. The WHO advises receiving at least two doses if a person has HIV or is immunocompromised, and three doses if practical[34].

Clinical practice is made more flexible by the HPV vaccine age range. The vaccine considered to be more effective, if administered before a sexual debut. To identify the ideal age to finish the immunization series, risk assessment and collaborative decision-making should be carried out for each patient[35].

Human Papillomavirus Prevalence in Bladder Carcinoma

HPV has been connected to increased risk of bladder cancer. The incidence of HPV cancer bladder patients varies greatly, ranging from 64.6% to total lack of the virus in tissues [1].

Research conducted worldwide to examine the etiological relationship between HPV and ovarian and bladder cancer has produced contradictory findings about HPV's role in oncogenesis[36].

Urinary bladder cancer is prevalent globally, with urothelial carcinoma (UC) being the most common, accounting for 90% of all cases, followed by SCC and AD, with higher frequency in males [37].

Over the past three decades, bladder carcinoma incidence has surged, prompting increased interest in identifying potential etiological agents, including smoking, industrial exposure, arsenic, chronic irritation, and bacterial and viral infections [38].

UC with squamous differentiation (UC/SCC) is a subtype of bladder cancer associated with HPV, characterized by focal squamous differentiation [39].

Studies on HPV infection's role in breast cancer are controversial, with a wide percentage of positive cases ranging from 0% to 80%. Some suggest HPV is a risk factor for urogenital system carcinoma and SCC of the urinary bladder [40].

Two hypotheses that point to a potential link between HPV and bladder cancer. First one is that the urethra may be a reservoir for the virus, and the second one may be epithelial tropism, which could explain the association, but may be weak in most cases [41].

Immunological Marker in Bladder Cancer

While innate immunity cells, including lymphoid populations, are recruited from the circulation due to tumor-related factors, dendritic cells, neutrophils, regulatory T cells, and myeloid derived suppressor cells (MDSCs) are important immune cell populations in the human bladder. [42].

Immunity mediated by T cells is crucial for boosting the anticancer response. The two primary T cell lineages are CD4+ and CD8+. According to preliminary findings, a good prognostic factor for initial melanoma lesions was the rapid infiltration of T cells. Similar information has now been discovered in other malignancies. including ovarian cancer, renal cell carcinoma (RCC), bladder cancer, colorectal cancer (CRC), and also other solid cancers.[43]

Tregs (FoxP3+veCD25+ve CD4 T cell), a type of regulatory, are recognized for promote tumors in various cancers. They can be thymic or induced by TGFβ and other immunosuppressive cytokines. Blocking IL-10 and TGFβ can reduce Treg induction in bladder cancer cells [44].

In cystectomy specimens, increased lifespan is correlated with greater FoxP3 cell expression. FoxP3 expression suggests that "true" Tregs have an anti-tumorigenic function, and their presence in urothelial malignancies likewise correlates with better survival. [45].

According to other studies, survival and FoxP3T regulatory cells are negatively correlated [46].

Tumor-associated macrophages (TAMs) are a significant immune cell population seen in tumors. Macrophages may have immune-suppressive (M2) or activating (M1) properties. It has previously been proposed that TAMs are M2-like. They have a significant impact on angiogenesis, tumor growth, and immunological suppression in addition to secreting a variety of cytokines[47]

Macrophages consistently found healthy human bladders have a pro-tumorigenic role, with high TAM counts linked to decreased survival and treatment response [48].

Macrophages, Known to have anti-tumor properties, most malignancies lose them, leading to decrease "M2" phenotype in TAMs, despite their anti-tumor functions in vitro [49].

M2 macrophages encourage the growth of tumors by their role as antigen-presenting cells, influencing tissue remodeling, tumor angiogenesis, and adaptive immune system function, as demonstrated in bladder cancer cell co-culture experiments [50].

In bladder cancer, a recent study revealed that tumors with high cytotoxic lymphocyte infiltration and low macrophage infiltration had better survival rates. This suggests that macrophages suppress adaptive immunosurveillance and produce a tumor-favoring microenvironment, which calls for therapeutic approaches to address this [51].

A diverse subset of immune cells known as tumor-infiltrating lymphocytes (TILs) are prevalent in malignancies of various origins. Other T-cell subtypes, including T-helper cells and regulatory T cells (Tregs), influence the activity of cytotoxic T lymphocytes (CTLs), the primary effector cells in anticancer T-cell immunity. The balance between the different T-cell subtypes involved determines the impact of a given immune response. Tumor infiltration by CTLs (CD8) and generally (CD3) has been demonstrated to increase survival in UC patients. [47].

Neutrophils, absent in healthy bladders, are abundant in cancer patients' circulation and bladder tumors, with neutrophil-to-lymphocyte ratio (NLR) studies exploring their potential as a prognostic sign for bladder cancer [52].

Circulating neutrophil in tumors is likely due to the release of cytokines (CXCL1, CXCL5, and IL-8) which are potent neutrophil chemoattractants. The urothelium releases IL-8 in healthy cells, but it overexpressed in human bladder cancer cell lines [53].

Furthermore, different subsets of tumor-associated lymphocytes (TALs) display a variety of roles. The primary function of CD8 T lymphocytes is to combat tumor cells. However, because CD4 T cells can both initiate and maintain CD8 lymphocyte anti-cancer immune responses and convert anti-tumor activity into pro-tumor activity, they are considered a two-edged immunologic weapon. [54].

Human neutrophil proteins1, 2, and 3 (HNPs1, 2, and 3), also known as a-defensins1, 2, and 3, are upregulated in the tumor microenvironment in bladder tissue. Defensins are one of antimicrobial peptides (AMPs) family including cysteine-rich peptides with three or four intra-molecular disulfide bonds. They are divided into three categories: α, β, and θ defensins. The first two are the most prevalent antimicrobial peptides in humans. Since HNPs stimulate the generation of cytokines and the activation of immune cells, they may also function as immunomodulatory molecules in addition to being strong antibacterial agents [55].

The direct mechanism of action of HNPs in bladder cancer remains to be elucidated. The indirect effects of HNPs 1–3 include stimulation of tumor cell proliferation and potentially tumor angiogenesis. This may be accomplished as a result of HNPs promoting cytokine release, stimulating monocytes, and inhibiting the fibrinolytic system. The HNPs found in cancer cells are primarily derived from tumor invading neutrophils and eosinophils[56].

CONCLUSION

Several risk factors are associated with bladder cancer. HPV is considered an important risk factor for many cancer as it has a viral oncoproteins, E6, and E7. They influence the cell cycle regulation, telomere maintenance, genomic stability, tumor suppressor pathways, and apoptosis. While the immune response defends the host by suppressing neoplastic growth, several immune cells, including neutrophils, macrophages, and T-lymphocytes, promote tumor development and progression. The levels of human neutrophil peptide-1, -2, and -3, produced by neutrophils, increase in bladder cancer and might promote tumor angiogenesis and growth.

Abbreviations

Human papillomavirus (HPV), Human papillomavirus (HPV), open reading frames (ORFs), long control region (LCR), upstream regulatory region (URR), noncoding region (NCR), early (E), late (L), retinoblastoma protein (pRB), reactive oxygen species (ROS), reactive nitrogen species (RNS), United States Preventative Services Task Force (USPSTF), Centers for Disease Control and Prevention (CDC), polymerase chain reaction (PCR), urothelial carcinoma (UC), UC with squamous differentiation (UC/SCC), renal cell carcinoma (RCC), bladder cancer, colorectal cancer (CRC), Tumor-associated macrophages (TAMs), tumor-infiltrating lymphocytes (TILs) , regulatory T cells (Tregs), cytotoxic T lymphocytes (CTLs), tumor-associated lymphocytes (TALs), Human neutrophil proteins1, 2, and 3 (HNPs1, 2, and 3), antimicrobial peptides (AMPs)

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