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Title: **Current Understanding in HPV-mediated Penile Carcinogenesis**

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Abstract

Human papillomavirus (HPV) is a prevalent condition with numerous implications on genitourinary health. While responsible for numerous benign conditions, it also plays a pivotal role in penile carcinogenesis. This review aims to discuss the current understanding of HPV in benign and malignant disease. Various aspects of the virus are discussed including high and low risk serotypes, molecular biology and pathogenesis mechanisms, as well as clinical manifestations. Finally, a discussion of current vaccination strategies is presented.

Introduction

Any understanding of penile cancer also requires an intimate appreciation of the relationship between the *human papilloma virus* (HPV) and penile carcinogenesis. While specific incidence estimates vary, numerous studies have described the incidence of concominant HPV infection with penile cancer to be between 30 and80%.[1,2] This relationship is also emphasized by the recognition of both HPV-mediated and non-mediated molecular pathways in the development of penile cancer. While the incidence of penile cancer in the United States and Europe remains less than 1% [2], the worldwide incidence has been established to be nearly 20 to 30 times greater in developed countries [1]. Considering these disparities, the impact of worldwide HPV infection on penile cancer is highly significant. Additionally, with the recent advent and continuing focus on HPV-related vaccination protocols, the prospect of prevention in a significant subset of penile cancer cases is encouraging. This review will focus on the HPV related significance in penile cancer. The aim is to present an updated review of the current literature regarding the role of HPV both in penile cancer as well as in penile intraepithelial neoplasia (PeIN). We will also discuss the current understanding of the current molecular pathways involved in the disease. Finally, recent vaccination approval and protocols will be outlined.

Human Papillomavirus

With over 170 types described [3], the HPV viruses represent a distinct group of double stranded viruses with particular propensity in human disease. The genome consists of a circular double stranded DNA with 800 nucleotide base pairs [4]. DNA sequencing

techniques have been able to divide the virus subtypes into several proposed subsets, based largely upon their typical route of pathogenesis as well as the underlying disease processes they clinically manifest as[3]. The alpha genus is of particular interest from a urological perspective, as this has been cited to include up to 30 various HPV isoforms with propensity for infection of the genital tract mucosa. [5] This includes both high and low risk isoforms, which will be further discussed later in this review.

Despite the numerous different HPV subtypes, from a molecular standpoint, there remains a high degree of genomic similarity. The virus itself is composed of an icosahedral capsid surrounding a nucleohistone core [6]. There are approximately 8 genes coded by the genome; "early genes"E1-E7, a non-coding region referred to as the long control region (LCR), and a region containing the L1 and L2 capsid proteins [3]. The E6 and E7 genes are believed to be the most highly conserved of all the HPV subtypes and have been implicated in the majority of cancer-associated subtypes. The influence of these genes on the molecular pathways of cancer development will be touched upon later in this review.

HPV implications in penile cancer precursor lesions

Penile precursor lesions can be subdivided between those, which are benign with little to no malignant potential, and those that may progress to invasive cancer. Conversely, HPV may also be divided into both "low" and "high" risk forms based on their oncogenic potential. The most common high risk HPV serotypes are 16 and 18 which are responsible for greater than 70% of all cervical and anogenital cancers in men and women [7]. In the cervical cancer literature, attempts have been made at sub-classification

of these types, as noted in the 2009 study by Bouvard et al. In that study, HPV types were divided into those considered carcinogenic, probably carcinogenic, and possibly carcinogenic. The carcinogenic types included high-risk (HR) types 16,18,31,33,35,39,45,51,52,56,58, and 59. [8] Conversely, the most common low risk (LR) HPV serotypes are 6 and 11 and have been cited as causing the majority of visible lesions.[7] This section aims to discuss the current understanding of the role of HPV in the following precursor lesions: Condyloma Acuminatum, Giant Condyloma Acuminatum (Buschke-Lowenstein Tumor), Bowenoid Papulosis, *Carcinoma in Situ* (Erythroplasia of Queyrat, Bowen's Disease), and Flat Penile Lesions (acetowhite lesions).

Condyloma Acuminatum

Condyloma acuminatum represents the commonly known clinical finding of genital warts, described as a non-tender frondular lesion that is spread frequently via direct skin to skin sexual contact[9]. These lesions, as previously noted, are most commonly caused by low risk HPVserotypes 6 (89%) and 11 (11%). They are associated with a high rate of spontaneous remission (30-40%)[7]. They are however highly contagious with a transmission rate of greater than 60% [7]. Genital warts form primarily on the penile glans and shaft on men [10]. Together, the low risk isoforms of HPV have an extremely low oncogenic potential, cited at approximately 5 to 10%[7]. In the landmark study performed in a Danish cohort by Bloomberg et al, approximately 50,000 male and female patients with the diagnosis of genital warts were evaluated over a twenty-year period. Comparing the observed versusexpected incidences, they estimated the impact of genital warts on various oral and anogenital cancer subtypes. In regard to penile cancer, a statistically

significant increase in the incidence of penile cancer was noted within one year of a genital warts diagnosis. This significance did not stand at any other time points analyzed [11]. However, this study was limited in this regard by the fact that only a total of 22 total patients with penile cancer were identified. Additionally, there was no pathological evaluation of the underlying HPV isotypes associated with a penile cancer diagnosis in these patients. Although there remains a small chance of risk of cancer progression with low risk HPV types, patients should be counseled that in the setting of condyloma acuminatum alone, the likelihood of progression is essentially zero and this should be considered a benign lesion.

Giant Condyloma Acuminatum

Giant condyloma acuminatum(formerly referred to as Buschke-Lowenstein Tumor) is a rare sexually transmitted disease. Described as a large, cauliflower-like mass found in the genital or anorectal region, it can be debilitating for patients and presents many challenges in management for clinicians. HPV isotypes 6 and 11 have been predominantly associated with its development, although other isotypes have been described in the literature in case reports [12]. Other risk factors cited for development of giant condyloma included chronic inflammation and a history of immunosuppression. This condition is noted for a greater than 60% recurrence rate as well as a greater than 50% likelihood of progression to invasive carcinoma [13] Importantly, it should also be noted that while it does carry high invasive potential, the likelihood of metastasis remains low [13]. Histologically, it is differentiated from ordinary condylomas due to its thickened stratum corneum, papillary projections, and its tendency to invade deeply as mentioned

earlier. Additionally, it is distinguished from malignant squamous cell carcinoma due mainly to its intact basement membrane [14]. Treatment generally consists of surgical resection and potential penile reconstruction. While not a tumor associated with widespread disease and mortality, giant condyloma acuminatum represents a distinct clinical entity from condyloma acuminatum with a direct relationship to HPV infection.

Bowenoid Papulosis

Bowenoid papulosis, also known as undifferentiated intraepithelial neoplasia, is a condition typically appreciated in younger men. Described as red-brown papules on the glans or shaft of the penis, it is generally considered benign. Histologically, it is characterized by full thickness cytological atypia, which may make it indistinguishable from other forms of squamous cell *carcinoma in situ*[4]. However, the final diagnosis is typically based on clinical findings.

HPV has a predominant role in the development of Bowenoid Papulosis, particularly isotypes 16, 18, 31, and 39 [15]. Although generally considered, benign, the association with high risk HPVisotypes has contributed to rare reports of development into invasive cancer. Treatment typically consists of close observation or topical treatment [9].

Carcinoma in Situ

Erythroplasia of Queyrat and Bowen's Disease both refer to forms of squamous intraepithelial neoplasia with a high rate of progression to invasive SCC (cited at 10-15% in some studies) [15].Erythroplasia of Queyrat has been described as having the highest likelihood for malignant progression [15]. It is also described as rare, contributing to less than 1% of male malignancies [16]. It is described as a well demarcated, flat, erythematous

plaque located on the penile glans or prepuce of uncircumcised men [9]. It is often associated with crusting, bleeding, or ulceration especially if it is invasive in nature[16]. As with SCC, there is a high association with HPV isotypes 16 and 18. A distinction with Erythroplasia of Queyrat lies in its association with HPVisotype 8. In a study by Wieland et al, biopsy specimens from eight patients with Erythroplasia of Queyrat were evaluated by polymerase chain reaction sequencing. While 88% of the specimens did show HPV isotype 16, HPV isotype 8 was detected in all specimens. Additionally, this isotype was not noted in controls of inflammatory, benign penile lesions, Bowen's disease samples, or cervical and vulvar cancer specimens. [17] Of note, HPV isotypes 39 and 51 were also identified in some of these specimens. The author's conclusions were that HPV isotype 8 coinfection may represent a distinct histopathological entity in regard to Erythroplasia of Queyrat. Additionally, it may represent a clinical tool in distinguishing it from Bowen's Disease [17].

Bowen's Disease, conversely, is described clinically as an area of scaly, velvety, erythematous patches on the penile shaft [18]. It is typically asymptomatic, although may at times be associated with pain. Histologically, it is characterized by full thickness epidermal atypia, disordered architecture, and abnormal mitoses [19]. Bowen's disease is associated with HPV isotypes 16 and 18 in approximately 70% of cases and is described as having an approximate 5% incidence of progression to SCC [15]. Treatment methods for both Bowen's disease and Erythroplasia of Queyrat are similar and include circumcision if applicable, topical therapies, and local excision

Flat Penile Lesions

A less often-discussed preneoplastic lesion is the flat penile lesion, or penile acetowhite

lesion. Clinically these lesions are distinct from the others previously discussed in that they are typically asymptomatic in addition to not being noted to the visible eye. They are typically located at the penile mucosal surface and become visible as a well-demarcated plaque area when stained with an acetic acid solution [20]. PCR detection methods have demonstrated that the presence of acetowhite lesions demonstrates a high concordance with alikelihood of HPV seropositivity [21]. Additionally, studies have demonstrated a positive association between the viral loads and HPV positivity in these patients. In a study by Bleeker et al., the presence of flat penile lesions as well as HPVseropositivity was studied in a population of men with no history of sexually transmitted infection as well as those with partners with a history of cervical intraepithelial neoplasia (CIN). Their study found a higher association with HPV seropositivity, viral loads, lesion diameter, and frequency of presentation in those patients with CIN positive partners [22]. Theoretically, male patients with higher viral loads could be at an increased risk of transmission to unknowing partners. These findings demonstrate the clinical challenge presented by this condition.

Molecular Pathways

The ability of HPV to infect healthy cells and potentially progress to carcinogenesis involves the complex interplay between the site of infection, ability to establish a productive viral lifestyle, and the ability to progress to malignant transformation. This section will discuss these points in greater depth.

Infection and Viral Life Cycle

HPV infection begins with epithelial trauma which permits for infection of an epithelial

basal cell with the virus [23]. After endosomal uptake, the viral DNA is transferred to the host nucleus. The viral genome is established in the host cell as a stable episome in cells of the basal layer [24]. The viral genome replicates during the S phase of cell division. It is during this portion that the E2 protein of the HPV genome has particular importance due to its anchoring of the viral episome to the host mitotic chromosomes [25]. The time between infection and the appearance of lesions varies. Experiments with canine HPV strains have suggested the appearance at 4 weeks post-infection [26] although some research suggests that initial viral titers and HPVserotype are important contributing factors .[27]

Cell proliferation is well understood and mediated by the E6 and E7 viral oncogenes [24]. The control of proteins normally involved in cell-cycle progression is controlled by the*retinoblastoma* protein (pRb) which associates with the E2F transcription factors in non-cycling cells .[24] Under normal situations, activation of the cyclin/CDK complexes leads to the phosphorylation of pRb and E2F release with subsequent protein expression. In HPV infection, the E7 protein complexes with pRb which leads tounregulated dissociation of E2F and protein expression. Under normal situations, although the feedback loop is bypassed, continued cell proliferation would lead to an increase in p53 expression and cell degradation. However, in the HPV proliferation cycle, particularly high risk HPV types, E6 forms an ubiquitin ligase with leads to p53 degradation and prevention of cell degradation.[24]An additional consideration between low risk and high risk HPV isoforms is the expression of p21 and p27 kinase inhibitors. If present in sufficient quantity, they will bind with E7 and other cyclin proteins, rendering them inactive.[28] In high risk forms, this is believed to be overcome by the high levels of E7

protein present in the viral genome.[24] An additional mechanism of cell proliferation in high-risk HPV serotypes involves E6 independent mediated proliferation via its terminal PDZ binding domain. E6 is believed to mediate suprabasal cell proliferation and may be important in the metastatic potential of some HPV related neoplasms.[29]

The progression to malignancy requires a complex interplay between continued viral genome expression, packaging, and release to promote infection. Some theories suggest that the progression to malignancy occurs after uncontrolled cell proliferation which ultimately leads to continued point mutations and ultimately carcinogenesis. However, this remains an area of debate and continued research[30].

HPV Vaccination for Penile Cancer

There are two currently Food and Drug Administration (FDA) approved vaccines for HPV in the United States.The quadrivalent vaccine protecting against HPV serotypes 6,11,16,and 18 which was FDA approved in 2006, initially for females[31]. It underwent approval for boys and young men aged 9-26 in October of 2009[32]. Most recently, the FDA approved an additional vaccineindicated for the prevention of cervical, vulvar, anal, and penile cancers caused by HPV serotypes 6,11,16,18,31,33,45,52, and 58[33]. It is indicated for females aged 9-26 and males aged 9-15. It is administered in a series of three shots given at 2 and 6 months apart[33].

The HPV vaccines contain virus like particle from one of the L1 outer particles of the strains they protect against.[34] These particles then assemble into the virus in a spherical confirmation. [35] This then leads to antibody production against the HPV serotypes. Antibody binding to the virus appears to inhibit its ability to enter the basal layer of the

epithelium cell it is attempt to infect. [36]Clinical trials of these vaccines have demonstrated safety and immunogenicity in men. [35]

The majority of data regarding the efficacy of the HPV vaccination programs comes to us from the cervical cancer literature[37].In this regard, data demonstrated a greater than 90% efficacy of both the bivalent and quadrivalent vaccine types againstcervical intraepithelial neoplasia. [37] However, initial data also suggested a poor efficacy against active or established infection, reaffirming the recommendations for vaccine administration prior to the initiation of sexual activity.

In 2011, a large double blinded placebo controlled trial was performed on over 4000 men ages 16-26 to assess the efficacy of the quadrivalent vaccine. End points included the prevention of extra-genital lesions caused by HPV serotypes 6,11,16, and 18. A total of 36 lesions were noted in the vaccine group compared to 89 in the placebo group[38]. An important distinction of this study was that the majority of the lesions in both the placebo and vaccine group were condyloma accuminata (77 and 28 patients, respectively-caused by low risk HPVserotypes). Nevertheless, this study did demonstrate the efficacy of the quadrivalent vaccine against all vaccine serotypes [38]. Despite the proven safety and efficacy of the currently available vaccines, there remain significant challenges in delivery including assuaging fears of local communities, cost issues, and logistics of identifying and effectively providing the vaccine in both high-risk and poorly accessible communities.

Conclusion

HPV has numerous implications in genitourinary health including both benign and

malignant conditions. This review has outlined the current understanding of HPV and its implications in penile carcinogenesis. With the recent advent of vaccinations aimed at prevention, the prospects are promising regarding decreasing the societal impact of HPV disease. While much work remains, continued establishment of organized vaccination programs along with continued deeper understanding of the molecular aspects of the disease can further attempts at its eradication.

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