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Human papilloma virus-related premalignant and malignant lesions of the cervix and anogenital tract in immunocompromised women

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ABSTRACT

The number of immunocompromised patients is rising, and immunodeficiency is an independent risk factor for the development of premalignant and malignant lesions of the cervix and anogenital tract. The aim of this review was to summarize and update data on human papilloma virus (HPV) infections and HPV-based anogenital lesions detected in patients who were immunocompromised due to both organ transplantation and human immunodeficiency virus (HIV) infection. The incidence of HPV infections among solid organ recipients and HIV positive females is reported to be significantly higher when compared with age-matched healthy controls- i.e. higher by up to 65% and 46.6% respectively, vs 38% in the controls. These infections are also more often chronic, high risk HPV and multitype. Data suggest that HPV infections in these patients might not only occur more frequently, but that the course of the infection might also lead to faster oncogenesis. However, the treatment options for malignancies are limited; and this implies the need for intense primary and secondary prevention regimens. As infections with HPV types other than 16 and 18 and multitype infections are particularly frequently discovered in immunocompromised patients, they would probably benefit most from a nonavalent vaccine. Gynecological screening should be performed annually, including cervical smears and/ or HPV testing. In the group of non-responders, self-sampling methods should be considered.

Key words: HPV; human papilloma virus; immunocompromise; HIV; transplantation; malignancy

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INTRODUCTION

For years, the greatest concern regarding patients treated with transplantation for end-stage organ failure was to sustain the graft function in order to lengthen patients' life expectancy. Nowadays, solid organ rejections are successfully prevented with maintenance treatment based on combinations of immunosuppressive drugs such as calcineurin inhibitors (cyclosporine, tacrolimus), corticosteroids and adjuvant drugs (mycophenolate mofetil, azathioprine or mammalian target of rapamycin-mTOR inhibitors *e.g.*, sirolimus, everolimus) thus improving patients' survival rates. Recent clinical observations indicate that life expectancy depends more on factors secondary to life-long immunosuppressive therapy and the increasing age of this transplant population, such as cardiovascular diseases or malignancies, and especially those driven by viral infections. It is estimated that in the next decade, mortality due to malignancies will exceed that from cardiovascular diseases in the population of renal transplant recipients [1].

Immunodeficiency is a well-established risk factor for developing *human papilloma virus* (HPV)-related premalignant and malignant lesions of the lower genital tract and anogenital region [2, 3]. HPV infections are frequently observed in the general population, with up to 80% of women reported as experiencing such infections during their lifetime. These infections are however usually transient, and authors estimate that about 70% of immunocompetent individuals are clear of the infection within 12 months, and 91% are clear within 24 months, with the mean duration of the infection between 8 and 13 months [4]. On the other hand, immunocompromised patients are prone to experiencing chronic HPV infections, and the reasons for this persistence are not fully understood.

Immunodeficiency (immunosuppression or immunocompromise) results from any of three main reasons: viral

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infections as in *human immunodeficiency virus* (HIV) positive patients or in patients with acquired immune deficiency syndrome (AIDS); from the use of immunosuppressive drugs by such as solid organ transplant recipients (*e.g.*, renal transplant recipients (RTRs), or liver transplant recipients (LTRs) and/or in patients with connective tissue diseases (*e.g.*, systemic lupus erythematosus, or systemic scleroderma); and also in rare cases of primary immunodeficiency disease. Immunodeficiency in both HIV/AIDS patients and solid organ recipients was proved to be an independent risk factor for developing various malignancies, including HPV-related malignancies [2]. Buell et al. [1] estimated that after 10 years of immunosuppression, the risk of malignancy reaches 20%, which is three- to fivefold higher than in the general population.

Hinten et al. [5], in a review published in 2012, analyzed HPV-related premalignant and malignant lesions of the female anogenital tract in RTRs. In our mini-review, we aimed to combine and update data on HPV infections and HPV-based anogenital lesions detected in immunocompromised patients due to both organ transplantation and HIV infection. To do this, we searched the PubMed database looking for information on "human papilloma virus" or "HPV" and "immunosuppression" or "immunodeficiency" or "transplantation" or "HIV" and "cancer" or "malignancy" or "neoplasia". References included in the articles thus retrieved were also reviewed to identify further articles corresponding with our analysis topic.

HUMAN PAPILLOMA VIRUS (HPV)

Over 200 types of HPV have been discovered so far; and we distinguish between cutaneous subtypes connected with the formation of verrucae and mucosal subtypes that are mostly responsible for the development of lesions in the anogenital region. The latter are further divided into low-risk HPV subtypes (lrHPV: 6, 11, 27, 32, 42, 53, 54, 57, 61, 62, 69, 71, 72, 81, 83, 84, 86, 87, 89, 90, 102, 106), high-risk HPV subtypes (hrHPV: 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66), and HPV subtypes of unknown risk (subtypes 26, 30, 34, 53, 67, 68, 69, 70, 73, 82, 85 and 97) that are further investigated to assess their oncogenic potential and that are usually considered to be potentially high-risk subtypes [6].

The most-studied subtypes that are linked with the creation of anogenital malignancies are hrHPV types 16 and 18, and they are said to be responsible for approximately 70% of cervical cancers and precancerous lesions [7]. Another 20% of cervical cancers are related to hrHPV types 31, 33, 35, 45, 52 and 58 [8]. Studies have shown that HIV infection might influence the carcinogenicity of hrHPV types and therefore, the detection rates of invasive cervical carcinoma attributable to HPV 16 might be lower in HIV-positive females, with concomitantly higher detection rates of cancers attributable to HPV 18. Some authors have claimed that acquisition of HPV 16 is less affected by the CD4 cell count than the acquisition of other hrHPV types; and this might indicate the existence of mechanisms that enable HPV 16 to avoid immune surveillance, and as such, it is something that requires further investigation [8].

INCIDENCE

The incidence of HPV infections among both solid organ recipients and HIV-positive females are reported to be significantly higher than among age-matched healthy controls: up to 65% and up to 46.6% vs 38% respectively [9, 10]. The infections are also more often hrHPV and multitype infections. Data suggest that HPV infections in these patients might not only occur more frequently, but that their course might also lead to faster oncogenesis [11]. It was proved in a study by Adebamowo et al., that HIV-positive females, when compared with HIV-negative subjects presented a significantly higher prevalence of lrHPV and hrHPV and a persistence of hrHPV [12]. These findings are supported by those of the meta-analysis by Looker et al., which proved that in the presence of HIV infection, the risk of HPV acquisition doubles, and for clearance halves, especially with a decline in the CD 4 cell count. A threatening observation is that similarly to other sexually transmitted diseases, HPV infection itself may promote the acquisition of HIV infection [7].

However, some authors found the prevalence of hrHPV infections and genital malignancies to be similar to that in healthy age-matched controls [13, 14] (Tab. 1).

Table 1. High-risk HPV prevalence

Article	Year		Reason for immunocompromise	Number of patients included	hrHPV detected	Most common hrHPV subtype
Adebamowo et al. [12]	2017	original	HIV +	427 (baseline) 321 (after 6 months)	124 (29%) 51 (15.9%) respectively	Type 52 (8.9%/ 5.5%) Type 35 (7.0%/4.4%)
Pietrzak et al. [13]	2012	original	RTRs	60	11 (15%)	—
Origoni et al. [14]	2011	original	RTRs/R&PTRs	48	10.5– 27.7 over 10 years of observation	—
Roensbo et al. [27]	2018	original	RTRs, BMTRs	60	15% (29.4%– BMTRs, 9.3% RTRs)	Type 45 (3.3%)

hrHPV — high risk human papilloma virus; RTRs — renal transplant recipients; R&PTRs — renal and pancreas transplant recipients; BMTR — bone marrow transplant recipients

Another important set of findings that often characterizes HPV, is that in immunodeficient females the related anogenital malignancies are multifocal, and that they may develop synchronously or metachronously. It has recently been suggested that multifocality in these patients might be due to repetitive independent infections with various HPV types. This thesis is supported by the fact that in contrast to the general population, in which such multifocal lesions usually contain identical HPV types, in immunocompromised females, multiple types of HPV are often detected, even including types that are not usually specific for high-grade lesions and the types may vary from lesion to lesion within the same person [11, 15]. Varying hrHPV subtypes between different lesions were reported in 57.1% of patients by Meeuwis et al. [11].

HPV PERSISTENCE

Persistent hrHPV infection is a factor that is necessary for the development and maintenance of dysplastic lesions and their further progression to becoming invasive anogenital cancers [16]. Studies with immunocompromised females show that these chronic infections are partially linked to viral latency. Studies on HIV-positive females have shown a significantly reduced likelihood of HPV infection being cleared when compared with HIV-negative patients; however not all the studies indicating this achieved sufficient statistical significance to make the findings conclusive [17].

Some studies suggest that in HIV-positive patients, there are additional factors, apart from immunosuppression, that contribute to the increased prevalence and persistence of HPV infections. This might be due to direct interactions of the viral genes of HIV and HPV or to changes in reactions of the cytokines in cervical mucus to HPV [12].

RISK FACTORS

The risk for developing malignancies is said to be linked to the dose and duration of immunosuppression treatments [1]. However, some authors suggest that the intensity of a specific immunosuppression treatment might constitute a more important factor in oncogenesis than cumulative doses [18]. A recently published study by Mazanowska et al. [19] suggests that an hrHPV infection's prevalence might also be influenced by the type of immunosuppressants administered. For instance, RTRs treated with mammalian target of rapamycin (mTOR) inhibitors may be less prone to developing cervical cancer than those on regimens that lack these drugs. Therefore, some authors state that graft recipients who are at a particularly high risk of developing malignancies could benefit from including mTOR inhibitors in their therapy [19]. The connection between the use of certain immunosuppressive drugs and the development of malignancies was also studied by Madeleine et al. [20].

LESIONS OF THE CERVIX

Infection with hrHPV is a necessary factor in the development of cervical intraepithelial neoplasia (CIN) and cervical cancer in both immunocompetent and immunocompromised individuals: the hrHPV incidence in squamous cell carcinoma (SCC) of the cervix is reported to be 100%. While the incidence of CIN in RTRs is shown to increase 2- to 14-fold, the incidence of invasive cervical cancer in RTRs, which was previously 3-to-5 times higher than in the general population, is now comparable, due to the implementation of early screening [3, 11].

The progression of abnormal cervical cytology in immunosuppressed females is observed to be more rapid than in healthy controls, while the regression rates in RTRs are significantly lower than in the general population. Tanaka et al. [21] reported 0% spontaneous regressions of CIN 1 and CIN2 in RTRs compared with 68% and 52% respectively in controls.

AIDS patients are defined as individuals who are HIV positive and have either a CD4 cell count below 200/μL and/or an AIDS-defining disease, and in 1993, cervical cancer became one such disease.

The prevalence of CIN among HIV-positive patients is estimated at about 20–40% compared with 3% in the general population [22]. Since 2008, British guidelines recommend offering an HIV test to all patients diagnosed with CIN2 or above.

Data on associations between the risk of developing cervical cancer and levels of immunosuppression as determined by the CD4 cell count, are inconclusive, as some authors observed an increased risk in patients with a lower CD4 cell count and others noted no such relation [23, 24].

The influence of highly active antiretroviral therapy (HAART) on HPV-related malignancies and HPV infection itself is also a matter of controversy. Some authors have reported an increased chance of regression of CIN and clearing of HPV infections other than types 16 and 18, while others observed no such correlation [10, 23].

VULVAR LESIONS

Histopathologically, most invasive vulvar cancers are squamous cell carcinomas (SCC). Together with SCC's preinvasive precursor, vulvar intraepithelial neoplasia (VIN), it may be derived either from an HPV-dependent pathway, or from an independent pathway. Unlike premalignant and malignant lesions of the cervix that are always connected with an hrHPV infection, and premalignant and malignant lesions of the anus in which the hrHPV infection rate is also very high, most vulvar SCC and VIN in the general population are hrHPV-free and are observed in women in their 70s, while HPV-positive vulvar lesions are less common (20–57%) and are observed more frequently among younger females. In contrast, the majority of vulvar SCC and VIN discovered among immunocompromised females are hrHPV-related;

and studies show that these might constitute up to 100% of cases. In this group of patients, the woman's age when vulvar cancer is diagnosed, is significantly lower than in healthy controls: approximately 40 years old; and this is a result of an HPV-dependent etiology [9, 11].

In a study by Meeuwis et al. [3], a 50-fold increased risk for developing vulvar SCC was detected in a cohort of RTRs. The study found that the most common HPV types in vulvar lesions in both immunocompetent and immunocompromised patients were type 16 (60% vs 50% respectively) and 33 (20% vs 17% respectively), while the other types described in vulvar lesions in the general population are 18, 52 and 58. Type 58 also occurred in 17% of the vulvar neoplasms of RTRs in the cohort studied by Meeuwis et al. [11]. Studies have shown that vulvar cancer usually develops between 10- and 20-years following transplantation, which might suggest that its development requires prolonged HPV infection [5].

A meta-analysis study by Grulich et al., comparing the incidence of malignancies between population of HIV/AIDS patients and solid organ recipients, suggested there is a higher risk of developing vulvar cancer in the latter population [2].

Interestingly, the incidence of VIN (but not invasive vulvar cancer) and anal intraepithelial neoplasia (AIN) in organ recipients was observed as increasing in patients who had received a transplant for the second time. The authors also noted a significant rise in the incidence of vulvar cancer in pancreas transplant recipients [20].

VAGINAL LESIONS

The number of vaginal intraepithelial neoplasia (VaIN) is observed to increase. These lesions are often diagnosed simultaneously to VIN and CIN [3].

ANAL LESIONS

Most anal cancers, in both immunocompetent and immunocompromised patients, are SCC. AIN is similar to CIN. Mostly, both invasive and preinvasive anal lesions are HPV-dependent; and therefore, immunocompromised patients are also at a higher risk of their development. In the general population, anal cancer constitutes about 1.5% of cancers, while in the cohort of RTRs studied by Meeuwis et al. [11], the increased risk of this cancer was estimated to be approximately 122-fold. Studies show that risk factors for developing anal cancer are anoreceptive intercourse, previous diagnosis of an HPV-related cervical or vulvar cancer, and condylomata acuminata.

The detection rate for HPV infections in invasive anal cancer is 71–92.2% in the general population [11]. HPV subtype 16 is the most prevalent, and is detected in 66.7% of patients, followed in prevalence by subtypes 18 and 33.

HIV-positive females are said to have a 35-fold higher chance of developing anal cancer when compared with HIV-negative controls. Also, in a meta-analysis by Grulich et al. [2], HIV/AIDS patients proved to be at a significantly higher risk of developing anal cancer when compared with subjects who were immunosuppressed because of solid organ transplantation.

Furthermore, a higher risk of developing anal high grade squamous intraepithelial lesions (HSIL) was observed in HIV positive patients who had undergone solid organ transplantation, regardless of the organ type transplanted or use of T cell depleting medications. No further studies have yet been performed on this group of patients [25].

PRIMARY PREVENTION

As the incidence of HPV infections, and the overall risk of developing HPV-related premalignant and malignant lesions of the anogenital region in immunocompromised females increases, actions should be taken in order to prevent these infections. Patients should be educated on anogenital cancer risk factors and vaccination should be recommended. The effectiveness of vaccination in anogenital cancer prevention in the general population is already well-proven. However, there is limited data on HPV vaccines in immunosuppressed females. The safety and immunogenicity of these vaccinations have already been proved in the population of HIV-1 infected women [26]. Further research is needed to determine whether vaccine-induced immunity against HPV persists in immunocompromised patients in contrast to vaccine-induced hepatitis B immunity which has been reported as declining over time in this group of patients [5]. Recently published data by Cespedes et al., on the response of HIV-1 positive females to a quadrivalent HPV vaccine, are promising. The data suggest that despite the gradual decline in antibody titers, seropositivity was sustained until 72 weeks post-vaccination for all subtypes except for type 18, in a cohort of patients with CD4 $\leq$ 200 cells/mm^3 [6].

Moreover, it is worth noting that as infections with hrHPV types other than subtype 16 and 18 and multitype infections are both discovered particularly frequently in immunocompromised patients, these patients would probably benefit most from the nonavalent vaccine against types 6, 11, 16, 18, 31, 33, 45, 52 and 58 that was approved in 2014 [27]. In a study by Cespedes et al. [6], the nine hrHPV types listed above accounted for 63% of cervical and 64% of anal HPV types detected.

Studies have also been conducted to assess the therapeutic effectiveness of HPV vaccinations in the population of immunosuppressed patients [28].

SECONDARY PREVENTION

Despite a lack of hard evidence, but due to a generally accepted increase in the prevalence of hrHPV infections and the higher risk of developing anogenital malignancies in

immunosuppressed females, both the American Society of Transplantation (in 2000) and the Expert Group on Renal Transplantation (in 2002), recommended annual cervical cancer screening, including Pap smears and pelvic examinations in this group of patients [29, 30]. According to the literature, insufficient annual screenings are being carried out: Kerkhoff et al. [31] described an overall 16% uptake of annual screenings in the Republic of Ireland and that in 26% of RTRs there was no screening at all. Similarly, in the Northern Ireland study by Courtney et al. [32], the overall uptake was 10% and 32% of RTRs had no screening. The uptake of cervical screening in underprivileged countries is clearly even lower. Nega et al. [28] reported a 10% lifetime uptake of cervical screening in Ethiopia among HIV positive females, and 93.4% of those were only screened after the diagnosis of HIV.

Some authors proclaim postponing the implementation of annual screenings until approximately 3 years following transplantation in patients with a normal pretransplantation screening result because most malignancies are detected several years after transplantation (*e.g.*, according to Meeuwis et al. [3], detection is 9 years after RT). This matter requires further investigation.

SELF-SAMPLING

As the participation of immunocompromised patients in gynecological screening has proved to be low, despite recommendations for annual checkups, a novel method of HPV testing based on self-sampling was recently introduced in order to increase the detection of anogenital malignancies. It has been shown that giving nonresponders the opportunity to self-collect the specimen for hrHPV testing has increased their willingness to participate in the screening program. Various self-collection devices were tested, such as tampons, brushes, lavages and swabs. While tampons seem to be the most preferred device (probably as patients are most familiar with them) according to some authors, the self-collection device most researchers recommend is the cervicovaginal brush. These latter have proved to be well-accepted by females, have demonstrated a greater sensitivity for CIN detection than swabs, require less processing than tampons, may be transported and stored in a dry state, in contrast to lavages, and may therefore be delivered by mail, thus expanding the participation possibilities for screening programs [33]. It was proved that the sensitivity of self-collected vaginal samples is comparable with that of cervical samples [34].

TREATMENT

When diagnosing a malignancy in an immunocompromised patient, healthcare providers face additional factors that need to be taken into consideration when planning a therapy. In solid organ recipients the possible therapeutic options are greatly influenced by the need to preserve the graft's function. This relates mostly to surgery and radiotherapy. The location of graft in the pelvis, especially in RTRs, limits both the possibility of radical surgery with extensive lymphadenectomy and of radiotherapy [35]. For these reasons, oncologic treatment of solid organ recipients often has to be limited and therefore, mortality rates among invasive cancer cases are high. This latter emphasizes the need for primary and secondary prevention that enable early stage detection of the malignancy.

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