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The role of viruses in the pathogenesis of skin cancer in patients with chronic kidney disease and kidney transplant recipients

Abstract

In patients with chronic kidney disease and after kidney transplantation, the risk of cancer increases significantly due to the impaired function of the immune system. It is caused by the presence of uremic toxins or the use of immunosuppressive drugs and recurrent infections. It was found that in both groups of patients the most common type of cancer are non-melanoma skin cancers and among them squamous cell carcinoma (sSCC). Viruses remain the key carcinogens in both sSCC and other primary skin cancers.

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Both chronic kidney disease (CKD) and immunosuppressive treatment following kidney transplantation (KTx) significantly increase the risk of developing cancer. In a large observational study involving approximately 3000 patients with CKD not requiring dialysis, cancer was diagnosed in 13.3% of subjects [1]. The risk of cancer in patients with end-stage kidney disease is almost double that in the general population, with the most prevalent types including renal carcinoma, cancers of the urinary tract and liver, as well as lymphomas [2]. The primary risk factors in this group of patients include the length of dialysis therapy as well as younger age of patients [3]. Several factors have been postulated to promote malignancy in chronically hemodialyzed patients in addition to the adverse effects of uremic toxins. The most important of these include impaired immune system function, recurrent infections, abnormal DNA damage repair, excessive production of reactive oxygen species, and vitamin D deficiency [4, 5]. Other risk factors include excess use of analgesics and aristocholic acids capable of causing renal failure in the course of so-called Balkan endemic nephropathy and participating in the pathogenesis of cancer [6]. A higher risk of malignancy has also been shown in patients who had received immunosuppressive treatment for glomerulonephritis. The incidence of malignancy rates was at 13% in patients treated with cyclophosphamide and/or rituximab as compared to 9.7% in those not receiving this type of therapy [7].

In the group of patients after KTx, the cancer risk continues to be increased, reaching a value as high as triple that observed in the general population due to new contributing factors being added to the increased risk originating from the period of end-stage kidney disease and hemodialysis therapy, primarily due to the use of immunosuppressive drugs [8]. Identification of drugs having the greatest oncogenic potential is difficult because relevant therapeutic regimens are based on at least two agents. However, an additional mechanism increasing the risk of cancer is also associated with immunosuppression, namely the activation of latent viruses and simultaneous impairment in the ability to eradicate new infections. In the first two years after KTx, the risk of lymphomas [mainly the post-transplant lymphoproliferative disorder (PTLD)

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associated with Epstein-Barr virus (EBV) infection/reactivation] is particularly increased. In a later post-KTx period, skin cancers may develop as the most common but not necessarily the most significant oncological problem in patients after solid organ transplantation, including kidney transplantation [4, 6]. A large analysis involving more than 20,000 KTx patients and 30,000 chronically hemodialyzed patients compared the incidence of cancer in two Scandinavian countries, Sweden and Denmark. Non-melanoma skin cancers (NMSCs) and non-Hodgkin lymphomas were found to be the most common types of cancer in both groups. The standardized incidence *ratio* (SIR) for NMSC in patients after KTx was similar in both populations: 44.7 (n = 994, 95% CI, 42–47.5) in Sweden and 41.5 (n = 445, 95% CI, 37.8–45.5) in Denmark. Among the hemodialyzed patients, the SIR for NMSC was 5.3 (n = 304, 95% CI, 4.7–5.9)] [9]. The risk of developing the mentioned cancers increases over time and reaches 7% one year after transplantation, 10–15% to 45% 10 years after transplantation, and up to 70% after 20 years of KTx-related immunosuppressive therapy [10]. The incidence of NMSC in kidney recipients is 100 times higher than in the general population. The increased risk of NMSC is mainly associated with long-term use of immunosuppressive drugs which enhance the oncogenic properties of other risk factors, particularly ultraviolet radiation from sunlight, and viral infections (Fig. 1). Other risk factors include the history of skin cancer, fair complexion or a particular skin phototype, smoking, and male gender [11]. In solid organ transplant recipients, including kidney transplant recipients, the most common NMSC is *squamous cell carcinoma* (sSCC), also known as *epidermoid carcinoma*, which accounts for up to 50% of all skin cancers, followed by *basal cell carcinoma* of the skin (sBCC). In the general population, this *ratio* is reversed, possibly reflecting different pathogenicity mechanisms responsible for the development of these cancers in immunocompetent individuals and recipients of solid organs [11, 12].

While capable of being successfully eliminated in most cases by surgical excision, sSCC has, however, a high propensity for recurrence, metastasis, and even fatal outcomes [14]. The risk factors for sSCC include *human papillomavirus* (HPV) infection in the first place. The International Agency of Research on Carcinoma (IARC) classifies carcinogens, including biological agents, into five categories based on their potential carcinogenicity. Group 1 includes agents for which sufficient evidence of carcinogenicity in both humans

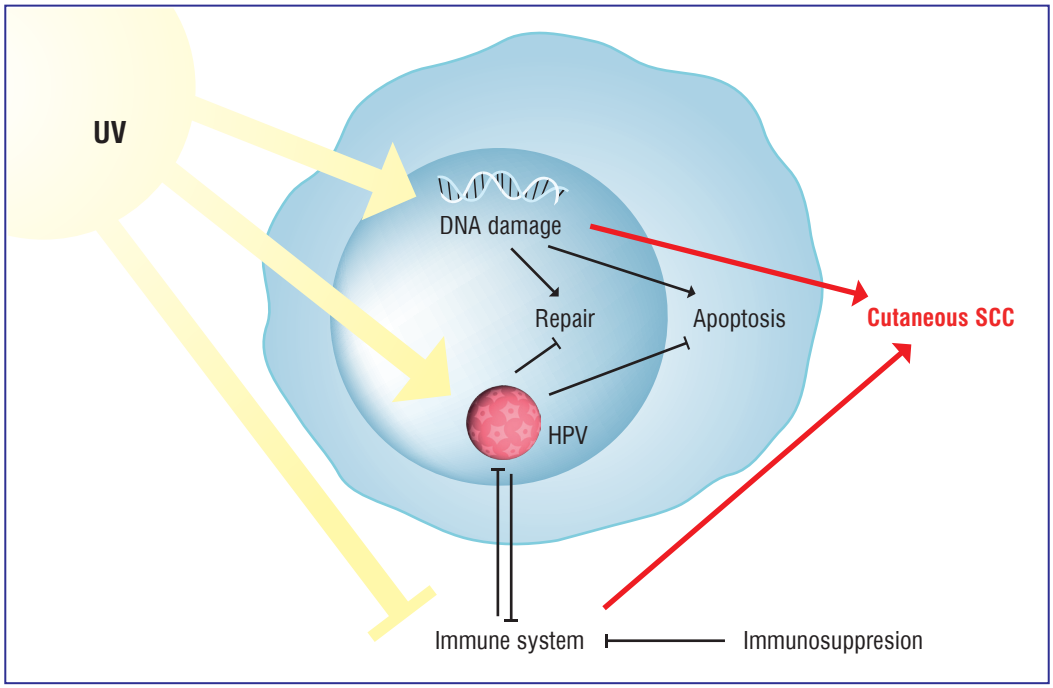

Figure 1. The role of risk factors responsible for the development of squamous cell carcinoma of the skin in solid organs recipients (compiled based on [13])

HPV — human papillomavirus, UV — ultraviolet radiation

and experimental animals is available, for example, the HPV types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, and the *human herpesvirus* 8 (HHV 8). Group 2A includes likely carcinogens for which limited evidence is available in humans while sufficient evidence has been obtained in experimental animals [as is the case with *Merkel cell polyomavirus* (MPV) and HPV68]. Group 2B includes potential carcinogens (such as HPV5 and HPV8 [15]). Viruses listed in Group 1 and MPV have a proven role in the pathogenesis of skin cancers in solid organ transplant recipients.

Human papillomavirus (HPV) represents a diverse group of viruses which mainly infect epithelial tissues and mucous membranes. Based on the sequence of the main L1 capsid gene, most of the more than 200 virus types characterized by date cluster within the alpha (α), beta (β), or gamma (γ) families. While a vast majority of α-HPVs are mucosal viruses isolated from the rectal and genital *epithelium*, some subtypes of this group (e.g., HPV 2, 3, and 10) as well as the β- and γ-HPVs were originally determined as cutaneous types [16].

The first mention of HPVs' association with papillary skin lesions presenting with carcinogenic potential dates to the early 1920s, following the discovery of *epidermodysplasia verruciformis* (EV), an inherited disease characterized by extensive formation of warts all over the body. At the time, EV patients infected with β-HPV 5 and 8 were found to be at higher risk of developing NMSCs, particularly in areas exposed to ultraviolet (UV) light. Taken together, the two viral subtypes are detected in about 90% of sSCC cases in EV patients. In these cases, β-HPV undergoes active transcription and generally persists in high copy numbers. As of today, β-HPV 5 and 8 are recognized by IARC as possible (group 2b) pathogenetic factors for the development of sSCC in immunocompromised EV patients [17].

The skin of most humans is infected with the entire spectrum of different cutaneous HPV types, their likely reservoir being the hair follicles. In the evolutionary process, cutaneous HPV types may have exploited different ecological niches in human skin tissues with cooperation occurring between HPV and host cells [18]. Specific triggers such as UV-induced DNA damage in sun-exposed cells, or immunosuppression and/or inactivation of the host-controlled viral life cycle (e.g., in EV patients) lead to enhanced HPV replication. The anti-apoptotic effect of cutaneous HPVs is a likely cause of keratinocytic damage, acting in synergy with UV radiation. Chronic viral infections result in the accumulation of further DNA mutations, presumably leading to cell immortalization. It therefore appears that cutaneous HPV types may be a factor in the early onset of sSCC. Unlike the subtypes found in the cervix, the genome of cutaneous HPV subtypes is generally not integrated into the host genome and persists extrachromosomally. In sSCC, significant viral counts, reaching 100–300 viral copies, were observed in cancer cells. However, it has also been found that not all cancer cells are infected with the virus [13]. The infectious cycle of the virus is linked to the process of keratinocyte differentiation. The virus enters keratinocytes within the basal layer through epidermal microtubules or hair follicles. Infection does not necessarily require the virus to have the virionic form, as skin abrasions and exposure to the naked viral genome can reproduce the entire natural history of infection. The naked viral genome is incorporated into the cell nucleus following a full mitotic cycle and replicated there in the form of episomes. The integrity of the genome and its proper segregation into daughter cells are ensured by viral proteins E1 and E2. Under normal circumstances, when keratinocytes migrate upward and start to differentiate, they stop replicating and undergo a series of changes until forming the *stratum corneum*. Viral proteins (E6 and E7) take over the checkpoint mechanisms and allow keratinocytes to enter a phase of uncontrolled proliferation while also being involved in epigenetic modulation, chromatin remodeling, and miRNA expression to promote dysregulation of tumor suppressor genes and oncogenes, and consequently transformation of keratinocytes [19, 20]. Finally, the E5 protein promotes proliferation, prevents apoptosis of infected cells, and probably facilitates further tumor growth [21]. All other proteins act as cofactors in this process. Following the differentiation of keratinocytes, proteins E6 and E7 are replaced by proteins E1, E2, E4, and E5, and the number of virus copies increases to the order of thousands per cell [22].

Two other NMSCs apparently involving viral infection as a factor contributing to their development include *Merkel cell carcinoma* (MCC) and *Kaposi's sarcoma* (KS). MCC is a rare, highly aggressive, and frequently fatal neuroendocrine skin cancer. Although it accounts for less than 1% of all cases

of skin cancer, this is the third most common cause of skin cancer-related deaths, after melanoma and sSCC [23]. MCC is a late complication of KTx, with a median onset time of about 5 years, its risk in transplant recipients being increased by a factor of 62 to 186 [24, 25]. In addition to immunocompromised patients, the high-risk group includes the elderly as well as those with HIV infections or hematological neoplasms [26]. In addition to UV radiation, infection with MPV from the family *Polyomaviridae* is an etiological factor for MCC. The carcinogenesis process in MCC is primarily linked to two major factors including clonal MPV integration and long-term UV exposure leading to DNA damage. MPV integrates into the genome of MCC cells, occurring early in the tumorigenesis process. In addition to integration into the host genome, chronic exposure to oncogenic viral proteins is another factor promoting tumorigenesis [17]. MPV infection can be contracted in childhood and the virus is detected in the skin in most healthy individuals. Despite the widespread and lifelong character of MPV infections, only a small percentage of the population develops MCC. Antibodies to MPV capsid proteins, especially immunoglobulin G (IgG), are detected in 60–80% of non-immunocompromised, healthy adults [27]. Immunosuppressive treatment remains the most important risk factor in KTx patients. Although the details of the effects of specific immunosuppressive drugs on the development of MCC following KTx are not fully known, calcineurin inhibitors and azathioprine have been established as factors contributing to the greatest increase in the risk of NMSC, including MCC. Calcineurin inhibitors have been shown to exert oncogenic effects by interfering with DNA repair, thus increasing the risk of NMSC. Pathophysiological links between the use of immunosuppressive drugs and the activity of MPV-positive and MPV-negative MCC are supported by the regression of MCC as observed after discontinuation of immunosuppressive drugs among kidney transplant patients who had developed metastatic MCC; the remission, however, did not last longer than 12 months [24–29].

Herpesvirus 8 (HHV8), otherwise known as *Kaposi's sarcoma herpesvirus*, is responsible for low-grade vascular proliferative lesions. HHV8 presents significant differences as compared to other types of herpesviruses, whose seroprevalence is almost universal among adults. For HHV8, seroprevalence has been established in the following areas:

1) high endemicity areas with seroprevalence of > 25% (including numerous regions of Africa);
2) intermediate endemicity areas with seroprevalence of 10–25% (e.g., the Mediterranean basin);
3) non-endemic areas with seroprevalence of < 10% [30].

Although seroprevalence is < 5% in the general population, it is much higher among men who have sex with men (MSM) (25–60% for HIV-positive MSM and 20–30% for HIV-negative MSM). The incidence of *Kaposi's Sarcoma* KS in transplant recipients can be up to 500 times higher than in healthy individuals. KS often develops early after transplantation, the time to disease onset after KTx ranging from 5 to 21 months. The incidence of KS in transplant recipients varies by geographic region and ranges from 0.5% in Western countries such as the US to 5.3% in Saudi Arabia [31]. The mechanism behind the development of KS has not yet been elucidated, although recent evidence suggests that it involves initial latent HHV-8 infection of endothelial cells followed by their conversion to spindle cells. The subsequent proliferative phase involves increased expression of a lytic cycle protein, the viral G protein-coupled receptor (vGPCR). In endothelial cells, the vGPCR oncoprotein stimulates the secretion of vascular endothelial growth factor (VEGF) and increases the expression of its receptor, fetal liver kinase-1/kinase domain receptor (Flk-1/KDR). This activation, along with other paracrine events, plays a key role in the ultimate development of the tumor [32].

Excessive *de novo* infections or latent virus activations underlie a significant proportion of NMSCs in solid organ transplant recipients. While these phenomena are impossible to prevent, proper selection of immunosuppressive therapy can reduce the risk of tumorigenesis as being predominantly induced by immune disorders.

In conclusion, human papillomavirus (and, in particular, some of its beta subtypes) is a recognized risk factor for skin cancer (first of all squamous cell carcinoma). Hemodialyzed patients, and particularly kidney transplant recipients present with a higher incidence of HPV, a populationally prevalent virus which in turn increases the risk of skin cancer in these

patients by up to 100–200 times. Human papillomavirus is a risk factor (cofactor) for UV-induced *squamous cell carcinoma* (SCC) of the skin. HPVs most likely play a role in the initiation of the tumorigenic process by reprogramming cell metabolism and resulting in phenotypic transformation. HPV-related proteins E6 and E7 play an important role in metabolic tuning while proteins E1 and E2 contribute to excessive proliferation of skin cells. A knowledge of the role of these proteins could be used in the future to develop new treatments for skin cancer. Human herpesvirus 8 (HHV8) is a pathogenetic factor for the development of Kaposi's sarcoma while Merkel cell polyomavirus (MPV) is involved in the pathogenesis of Merkel cell carcinoma. Skin cancer registries (as having been kept for many years in some countries) as well as appropriate prevention and education of nephrological patients (especially after organ transplantation) are very important. Patient education including perpetual reminders about the need to avoid UV exposure, wear protective clothing, and use high-SPF sunscreens is essential to reduce the risk of NMSC. Still, however, only 11.5% of kidney transplant recipients have been shown to be fully aware of the risk of skin cancer, the causes of skin cancer, and possible prevention options [11].

The presented work is an updated summary of the highlights from the presentation given during the session on the role of viruses in skin cancer in SOTRs held as part of the 3rd Scientific and Training Conference "Nephrooncology" in Gdansk on October 14–15, 2022.

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A.W. — conceptual contribution, substantive development of the text, selection of literature
J.M. — writing and updating of the text, final corrections

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