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Review

Skin Cancers in Kidney Transplant Recipients

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Abstract

Immunosuppressive therapy exposes kidney transplant recipients (KTRs) to increased risk of infections, cardiovascular diseases and cancers. Nonmelanoma skin cancer is the most common malignancy after kidney transplantation with the squamous cell carcinoma (SCC) being the most prevalent type. Increased incidence of cancer is associated with duration and degree of immunosuppressive therapy. It affects mechanisms of DNA repair which leads to altered DNA and carcinogenesis. Also, UV radiation, causing genetic mutations, plays a major role in DNA impairment. Increased risk for viral infections can lead to viral oncogenesis, especially of Human papillomavirus (HPV). The immune system cannot control the HPV infection which makes it persistent and leads to cancer. About 80% of SCC are linked with HPV. The Merkel cell polyomavirus is connected with development of Merkel cell carcinoma, herpes virus type 8 is associated with Kaposi sarcoma- all more common in renal transplant patients than in the general population. To minimize the risk of carcinogenesis but at the same time prevent graft rejection, it is advisable to reduce the dose of immunosuppression therapy. Moreover, switching from calcineurin inhibitor to mTOR inhibitor has promising effects on lowering skin cancer risk. It is recommended to do a dermatological screening before transplantation. Regular posttransplant dermatology visits and sun-protective behaviour are by now the only effective way to detect cancer at an early stage.

Keywords: skin cancer, kidney transplant, immunosuppression, oncogenic virus

Introduction

Kidney transplantation is the most frequent solid organ transplantation worldwide with total of 90,306 transplantations in 2018 [1]. To minimize the risk of graft rejection, patients need to take lifelong immunosuppressive therapy. However, this makes patients susceptible to infections, cardiovascular diseases and malignancies, especially skin cancer [2]. Skin cancer is the most common malignancy after kidney transplantation [3]. Kidney transplant recipients (KTRs) are at a higher risk of developing cancer than the immunocompetent population and it is also known that cancers in kidney-transplanted population are more aggressive [4]. The most common type of skin cancer in transplanted population is squamous cell carcinoma, whereas in general population leads the basal cell carcinoma [5]. Cancer is the second most common cause of death in KTRs after cardiovascular disease [6].

Histopathological examination is essential for diagnosis and therapeutic approach. This review deals with the development of skin cancers in patients after kidney transplantation, pathogenesis, immunosuppression and possible prevention strategies based on available literature (ClinicalKey, PubMed and UpToDate).

Incidence and risk factors

Skin cancer is the most frequent posttransplant malignancy and nonmelanoma skin cancer (NMSC) represents 95% of posttransplant skin cancer [7]. The incidence of skin cancer in organ transplant recipients in the United States of America has been reported at 1427 per 100,000 person-years [8].

Incidence of skin cancer in KTR increases with time posttransplant due to long-term immunosuppressive therapy [8]. While for basal cell carcinoma (BCC) risk increases linearly, for squamous cell carcinoma (SCC) risk increases exponentially with posttransplant survival time [9]. In the transplant recipients the overall ratio of BCC: SCC is 1:4 [10]. In non-transplant population younger than 30 years BCC:SCC ratio is 3.5:1, while in 60 years and older reaches 2:1 [11]. In Oxford Transplant Centre, the cumulative incidence of skin cancer is 61% 20 years after kidney transplantation [12]. For BCC in KTRs, the cumulative incidence is 14% after 20 years [13]. SCC starts to develop about 3 to 5 years posttransplantation [14].

The time that passed from kidney transplantation to diagnosis of the first BCC is 11.1±6.3 years. (15) Study

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by Harwood *et al.* reported that BCC usually occurs in male organ transplant recipients (OTRs) at younger age [16]. Opposite of that, study by *Mertz et al.* finds BCC predominately in female KTRs, in ratio of 3.3:1 and in earlier age than in males, what may be connected with higher UV exposure [15].
In the general population basal cell carcinoma is the most common type of NMSC and SCC is the second most common type of NMSC. In the transplant population SCC takes the first place [2]. Organ transplantation increases the risk of SCC by 65-200 times and BCC by 10-15 times [17]. SCC occurs at least 25 times more frequently than in the general population. SCCs are found to be more aggressive in transplant recipients, with higher recurrence rates and metastasis potential [18].
A study from the Transplant Skin Cancer Network from 26 centers with more than 10,000 patients identified the following statistically significant risk factors for posttransplant skin cancer (Table 1) [8].

Table 1. Significant Risk Factors for Development of Skin Cancer in Organ Transplant Patients (including: Heart, Lung, Kidney, Liver)

Pretransplant skin cancer
Male sex
White race
Age at transplantation 50 years or older

The incidence of melanoma in solid organ posttransplant patients is still in doubt. While some studies demonstrated 2.1 fold to 8 fold higher risk compared with the general population, others did not find increased risk [20]. In KTRs one large study found a 3.6 fold increased risk for melanoma [21].
Other risk factors for development of skin cancer in KTRs are UV radiation, intensity of immunosuppression and use of calcineurin inhibitors (CNIs) versus mammalian target of rapamycin inhibitor (mTORi) [22].

Pathogenesis

The pathogenesis of NMSC in KTRs is multifactorial. Increased incidence of cancer, especially of NMSC in KTRs is directly associated with duration and degree of immunosuppressive therapy [23]. The goal in KTRs is to maintain low kidney rejection rates, while not raising malignancy rates. Immunosuppressive therapy has a negative effect on immune surveillance. It affects deoxyribonucleic acid (DNA) repair mechanisms resulting in altered DNA and carcinogenesis. Immunosuppressive treatment also inhibits Langerhans cells [24].
Innate and adaptive immunity play a major role in cancer development. Natural killer (NK) cells are found to have a protective role in the control of tumor growth and dissemination, as well as tumor specific T cells [25]. T regulatory cells (Treg) Foxp3+ participate in appearance and proliferation of SCC, therefore we can conclude there is a correlation between the number of cells-NK and Treg Foxp3+ and the risk of SCC development [26]. NK lymphopenia and CD4 lymphocytopenia are risk factors for SCC in KTRs [27].
Calcineurin inhibitors (CNIs) are immunosuppressive agents used after kidney transplantation, some of which are cyclosporine and tacrolimus. They selectively inhibit calcineurin, thus suppressing the T cell activation [28]. CNIs might induce carcinogenesis in several ways such as increasing the production of TGF β, increasing the expression of VEGF and also by inhibiting apoptosis and DNA repair in immunocompromised host [20].
Antimetabolic agents are also used in immunosuppression therapy. They interfere with the nucleic acids' synthesis and inhibit T and B cell proliferation [29]. Mycophenolate mofetil (MMF) or mycophenolate sodium (MFS) and azathioprine belong to this group. Azathioprine may also be carcinogenic and its carcinogenic potential is probably associated with impaired DNA mismatch repair and microsatellite instability [30, 31]. Azathioprine is also associated with a selective UV-A photosensitivity generating chronic oxidative stress [32]. MMF has better efficacy and less possibility of developing skin cancer, although it has carcinogenic potential [33]. According to Sarah Yusuf *et al.* [33] MMF is more linked to the development of basal cell carcinoma than squamous cell carcinoma. Also, the subtypes of these tumors are not aggressive forms.
While KTRs on CNI and azathioprine are more likely to develop malignancy, KTRs treated with mTORi have significantly lower risk of NMSC and malignancies in general [34]. Conversing patient to mTORi, in a period of a year, leads to significant functional improvement of antitumor T cells [26].
UV radiation causes genetic mutations and a decrease in the density of epidermal Langerhans cells leading to local immunodeficiency [35]. UVB is more likely to induce skin cancer than UVA, at least in animal models [36]. Melanocytes are responsible for protecting DNA damage by melanin synthesis. Because of low pigmentation capacity, there is more chance for skin cancer development in white Caucasians [36]. For example, in African American kidney transplant recipients, lower incidence is found compared with white Americans [22]. Characteristic type of mutation is found in SCC in p53 tumor suppressor gene causing uncontrollable cell proliferation [22]. The mentioned mutation is a result of cytosine to thiamine transitions through the formation of cyclobutane dimers [31]. In BCC, pathogenic pathway are mutations in Hedgehog pathway related genes, like PTCH1 [36]. In the healthy population, the immune system would recognize and eliminate precancer, but in KTRs the immune system is under suppression causing cancer advancement.
KTRs due to long-term immunosuppressive therapy are at increased risk for viral infections, either new or reactivating latent which can lead to viral oncogenesis. NMSC in KTRs is connected with human papilloma-

virus infection, while their immune system is not able to eradicate an infection [37]. In KTRs with SCC greater quantities of HPV DNA are found [7]. Carcinogenesis of HPV is provided by its oncoproteins E6 and E7 that bind to p53 and pRB tumor suppressor proteins included in the regulation of cell cycle.
Most of the studies have shown that reducing or stopping immunosuppression can lead to regression of certain virus-associated cancers and skin cancers [38]. On the other hand, minimization of immunosuppressive therapy could lead to transplant rejection.
There is a correlation between a history of pretransplant skin cancer and risk of developing subsequent skin cancer in KTRs [3].
Smoking does not significantly influence the risk of skin cancer in KTRs [39]. Older age at transplantation increases the risk for NMSC development [40].

What is the role of DNA methylation of T cells?

Immunosuppressive therapy suppresses the activity of T cells, which have an important role in anti-tumor immune surveillance (CD8+), but can also provide an immune-tolerant environment for the tumor (CD4+). (41) DNA methylation is an epigenetic mechanism of regulation of cellular function. Peters FS *et al.* [41] researched differentially methylated regions (DMRs) in T cells involved in *de novo* posttransplant squamous cell carcinoma development. Analysing the samples collected before transplantation, they compared patients who developed SCC after transplantation to patients without SCC.
They found 16 regions significantly differentially methylated between the patients who developed SCC and those who did not, which may demonstrate that T cells of patients with posttransplant SCC have different DNA methylation profiles compared to the T cells of kidney transplant patients without SCC [41]. This gives the potential of studying DNA methylation of the T cells to possibly identify patients who are at risk for posttransplant SCC.
In another study, Peters FS *et al.* [42] found higher methylation of *SERPINB9* region in circulating T cells in patients with posttransplant cutaneous squamous cell carcinoma. *SERPINB9* gene encodes serpinB9 protein, which is a serine protease inhibitor that inhibits granzyme B, a serine protease found in granules of natural killer cells (NK cells) and cytotoxic T cells (CD8+). Granzyme B protein is necessary for target cell apoptosis in cell-mediated immune response. SerpinB9 is expressed by the cytotoxic T cells that protect themselves from granzyme B activity. It makes T cells stronger and more potent cancer cell killers, so the lower expression of serpinB9 has a potential role as a risk factor for skin cancer in patients with kidney transplant [42].

Types of skin malignancies in renal transplant patients

Nonmelanoma skin cancer (NMSC) represents 95% of posttransplant skin cancer. Risk factors contributing to the development of NMSCs in organ transplant recipients (OTRs) include a past medical history of any previous skin cancer, a personal history of significant sun exposure and a fair skin complexion or phototype. Further, greater immunosuppressive medication levels lead to an increased risk of NMSCs. Among immunosuppressants, specific older agents such as azathioprine and cyclosporine may increase the risk of developing NMSCs in contrast to newer agents such as sirolimus [43]. The most common types are BCC and SCC. Patients with squamous cell carcinoma present with erythematous, keratotic plaques with or without ulcer. SCC can occur on any part of the body, but it usually appears on sun-exposed sites such as face, which is the most common localization in older patients [31]. In organ transplant recipients (OTRs) SCC can be often found on hands ("transplant hands") and scalp ("transplant scalp"). SCC in younger OTRs is mainly located on the chest [44]. SCCs metastasize to the lymph nodes and can be aggressive. The risk of metastases in SCC in the general population is 0.5 to 5%. The risk increases to 8% for KTRs [19].
BCC looks like pink pearly papules, sometimes also presenting with ulcer. The most frequent location for this lesions is on the nose [45]. Moreover, BCC is best known for being locally aggressive which causes destruction.
Melanoma is an immunogenic cutaneous malignancy with higher risk of metastases, and its incidence continues to increase. It is important to know that the correlation between a risk of developing melanoma and an organ transplantation is less clear than that for NMSC [23]. There are several types of melanoma including: superficial spreading, lentigo maligna, nodular, and acral lentiginous. The 'ABCDE' acronym stands for a few changes that might indicate a melanoma (asymmetry, border irregularity, color variation, diameter more than 6 mm and evolution). Risk factors for developing melanoma, especially in renal transplant patients, include older age, male sex, recipient white race, less than four human leukocyte antigens (HLA) mismatches, living donors, and sirolimus and cyclosporine therapy. Importance of immunity role in melanoma pathogenesis is shown in the case report of a renal transplant patient who developed metastatic melanoma from a kidney donor [46].
Merkel cell carcinoma (MCC) is a rare and highly aggressive neuroendocrine tumor of the skin. MCC is thought to originate from the nerve-associated Merkel cell touch receptors, which are in the basal cells layer at the deepest portion of the epidermis. MCC tends to develop 7 to 8 years posttransplant. Reduction of immuno-

suppression may be recommended in OTRs who develop MCC [7]. Lesions are usually on the head and neck, presenting as dome-shaped pinkish-red to bluish-brown papules or nodules and are frequently ulcerated [23].

Can viruses lead to skin cancer in renal transplant recipients?

As we know, Human papillomavirus (HPV) is double-stranded DNA virus that belongs to Papillomaviridae family. There are more than 100 types of HPV [47]. Out of these, there are low-risk (6 and 11) and high-risk types [16,18,31,33,35,39,45,51,52,56,58,59,68,73,82] depending on their oncogenic potential. HPV selectively affects cutaneous and also mucosal membranes in different sites of the body [48]. Clinical manifestations of low-malignant potential types include cutaneous and anogenital warts. On the other hand, high-malignant potential types cause penile, vulvular and vaginal squamous cell carcinoma [48].

HPV is considered to be very common among renal transplant recipients because of the immunosuppression and low cell-mediated immunity (CMI). Because of the ineffective cell-mediated immunity (CMI), transplant recipients cannot control HPV infection. This can lead to persistent infection and increase the possibility of getting cancer [48]. Furthermore, transplant recipients get HPV associated cancer at an earlier age. Even 80% of squamous cell carcinomas are associated with HPV [49]. On the contrary, there is only 40% of SCC linked to HPV in immunocompetent individuals. When it comes to carcinogenesis, HPV of the beta genus (HPV-β) is included in the pathogenesis of posttransplant SCCs. The expression of E6 and E7 HPV oncogenes is necessary for malignant conversion [50].

Prevention includes three prophylactic HPV vaccines. First is Cervarix, a bivalent vaccine that targets types 16 and 18. Secondly Gardasil, a quadrivalent vaccine, targeting types 6, 11, 16 and 18 and lastly, Gardasil 9 which covers the same types as in the quadrivalent vaccine and 5 additional types (high-risk HPV types 31,33,45,52,28) [48].

The Merkel cell polyomavirus (MCPyV) was discovered in 2008 in Pittsburgh, Pennsylvania. It is small, circular, nonenveloped, double-stranded DNA virus that integrates into the tumor's genome [51]. This virus is responsible for development of Merkel cell carcinoma, highly aggressive and relatively rare skin cancer. The viral genome is divided into 3 main regions: non-coding regulatory region (NCRR), early coding region and the late coding region. The early region encodes the small T (sT) antigen and the large T (LT) antigen [52]. LT antigen plays a very important role in carcinogenesis. It inhibits retinoblastoma tumor suppressor genes, promotes cell division and is expressed in all of the tumor cells. MCPyV is also a part of the human skin microbiome [53]. Many people were exposed to MCPyV and did ddnot get MCC which only means that immunosuppression contributes to viral integration, mutagenesis and carcinogenesis.

Kaposi sarcoma (KS) is a vascular tumor caused by herpesvirus type 8 (HHV8) causing red or purple patches of abnormal tissue to grow under the skin. Although KS gained public attention as an AIDS-defining malignancy, it is also common among renal transplant patients [54]. The incidence is 400-500 times higher in renal transplant recipients than non-immunosuppressed population and it is responsible for approximately 3-5% of transplant malignancies [55]. The highest incidence is in the first year after transplantation, often presenting in an early period after transplantation (2-24 months). Specific locations for KS to disseminate are the trachea, lungs and gastrointestinal tract [56].

Management and treatment

The management of NMSCs in solid organ transplant recipients (OTRs) presents a variety of clinical challenges for physicians. Early skin biopsy and treatment of premalignant and malignant lesions are essential for treating these patients successfully [43]. Treatment for NMSCs includes topical therapies (5-fluorouracil 5% cream and imiquimod), photodynamic therapy (PDT) and surgical management. For metastatic SCC, medical, surgical, and radiation therapies should be combined. For patients who are not candidates for an operation, have lesions that cannot be completely excised or have perineural invasion, radiotherapeutical approach should be considered [57]. In addition, for metastatic BCC in OTRs, there is a Food and Drug Administration-approved medication, vismodegib. Vismodegib is a smoothened inhibitor in the sonic hedgehog pathway. Melanoma and MCC should be managed surgically with wide local excision with consideration of a sentinel lymph node biopsy based on the severity of the tumor. In life-threatening melanoma, immunosuppression changes and/or reduction should also be considered [23].

The mammalian target of rapamycin (mTOR) is a regulator of cell growth and survival, and it is often dysregulated in tumors. Switching from a calcineurin inhibitor to mTOR inhibitor, such as sirolimus can have promising effects on lowering skin cancer risk [58]. In KTRs on sirolimus there was a 56% reduction in the risk of NMSC [59]. Sirolimus and everolimus inhibit T and B cell activation by cytokines which prevents proliferation of the cell cycle. On the other hand, calcineurin inhibitors block the production of cytokines [60]. mTOR inhibitors have a potential effect on reducing the posttransplant malignancies associated with viruses [61]. The use of sirolimus can lower the risk of recurrent nonmelanoma skin cancer and bring to complete remission of Kaposi sarcoma [62]. A five-year randomized trial showed no difference in kidney rejection or mortality between sirolimus-based and calcineurin

inhibitors-based KTRs [63]. If needed, combining an mTOR inhibitor with reduced dose of calcineurin inhibitor could provide more sufficient immunosuppression and at the same time, reduce the risk of nephrotoxicity linked with calcineurin inhibitors [62].
Although mTOR inhibitors have certain side-effects (hypertension, hyperlipidaemia, pulmonary toxicity, delayed wound healing, leukopenia, thrombocytopenia and anemia) they should be considered as a secondary prevention of skin cancer development.

Education is prevention

Before transplantation a dermatological screening is recommended. All suspicious lesions should be excised and pathologically examined. Viral warts should be treated [64].
For transplant patients it is crucial to be conscious and sun-smart. The incidence of skin cancers may be greatly reduced by following some preventative measures whenever out of doors, for example: wearing sunscreen (for details about ideal features of the sunscreen itself as well as the routine of applying it, see the Figure 1 below), avoiding sun exposure (of special importance during the middle of the day, between 11 am and 4 pm, when UV radiation levels are at their highest); if you tend to do outdoor activities during these times, stay in the shade. Checking the weather forecast to find out ultraviolet index is an advisable habit to implement, covering up well (wear long-sleeved shirts and pants). Dark coloured, tightly woven materials provide the most UV protection. If possible, try to wear sun protective clothing that has an Ultraviolet Protection Factor (UPF) rating of 40-50+, wearing a hat when outdoors, wearing sunglasses (this provides the best protection to the delicate skin around the eyes-hence choose glasses that are close fitting with large lenses).
Health care personnel should educate their patients about skin cancers, the risks of sun exposure and new habits which they should incorporate into their lives. Studies have shown that patients who are well informed about their condition are paying more attention to lifestyle risk modification and are prone to sticking to the routine regarding positive sun-protective behaviour [65,66].
Measures as simple as showing patients instructive video material followed up by a questionnaire to assess their knowledge has been proven to be a successful method for the patients to retain positive sun-protective behaviour over the long haul [66]. If KTR is strictly avoiding sunlight, vitamin D deficiency may occur. Therefore, vitamin D supplementation should be considered [67].
KTRs are subjected to more frequent dermatology visits, because it is by now only effective way to detect cancer in the early stage and thereby provide successful treatment. In the first year of transplantation, KTRs should

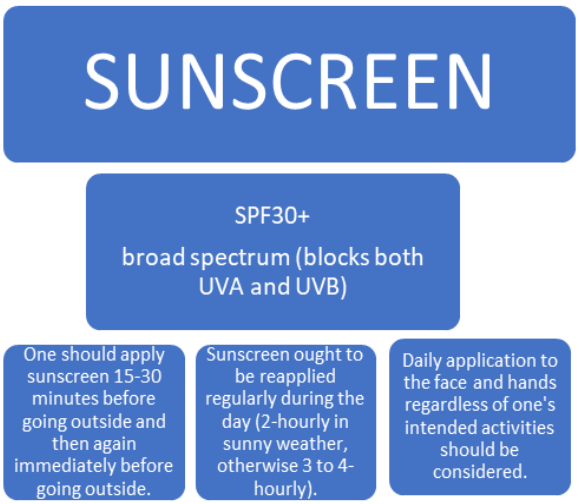

Fig. 1. What each patient should know about sunscreen

undergo a total body skin examination (TBSE) by a dermatologist and continue at least annually evaluation [68]. KTRs with a history of skin cancer should be followed closely. Skin self-examination is recommended.
When it comes to treatments that could possibly prevent nonmelanoma skin cancer, there is not enough evidence for their efficacy and safety [69]. Some of them are retinoids (such as acitretin), imiquimod, photodynamic therapy and nicotinamide (vitamin B3) [69]. Treatment with capecitabine, orally-administred prodrug of 5-fluorouracil, significantly decreases the incidence rates of recurrent SCC, BCC and actinic keratosis in KTRs and may be considered as a secondary prevention [70].
Reduced immunosuppression dose may decrease the development of nonmelanoma skin cancer, but also increase acute graft rejection [71]. As already mentioned, use of mTOR inhibitors is suggested, especially in KTRs with a history of skin cancer [68].
There are some clinical markers that could help physicians distinguish patients who are at a higher risk of posttransplant cancer development. A UK study of renal transplant recipients developed a predictive index of skin cancer risk that includes sex, age at transplantation and eye color, and it was able to identify patients who later developed nonmelanoma skin cancer with 80% sensitivity and 75% specificity [72]. Type of immunosuppression, its dosage and duration are related with the severity of posttransplant cancer [73]. A study from Oxford Transplant Centre showed that KTRs displaying high levels of CD57 CD8+ are at increased risk of squamous cell carcinoma development [74].

Conclusion

Skin cancer is one of the major causes of morbidity and mortality in patients with kidney transplant compared

to the general population. Due to severe immunosuppression that affects DNA repairing mechnisms, reactivation of potential oncogenic viruses and other risk factors, kidney transplant recipients are at a higher risk of developing malignancies. There are still challenges associated with the adequate immunosuppression therapy usage that is efficient enough to prevent a graft rejection, but also not having a carcinogenic potential. It is important to educate patients about skin cancer, make them well aware of potential risks and provide them a regular cancer screening.

Conflict of interest statement. None declared.

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