SKIN CANCER IN ORGAN TRANSPLANT PATIENTS - EPIDEMIOLOGY AND RISK FACTORS

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INTRODUCTION

Skin cancers are the commonest malignancies seen in organ transplant recipients (OTRs) due to the permanent need for immunosuppression (Euvrard et al., 2003; Ulrich et al., 2004), 95% of which are nonmelanoma skin cancers (NMSC), namely squamous cell carcinomas (SCC) and basal cell carcinomas (BCC). Other frequently seen skin cancers include Kaposi sarcoma (KS), Merkel cell carcinoma (MCC), and malignant melanoma (MM) (Mittal & Colegio, 2017). Whilst in the general population the incidence of BCC is greater than that of SCC, OTRs show a reversal of this ratio (Ulrich et al., 2008). Immunosuppressants have such a significant role that OTRs are 65 to 250 times more likely to develop SCC for example, when compared to the general population (Lindelöf et al., 2000).

Approximately half of all malignancies seen in patients following a solid organ transplant are in fact skin cancers, and these are more severe when compared to skin cancers in non-transplant patients, as they are more aggressive and tend to metastasize early (Greenberg & Zwald, 2011). In OTRs, the sensation of pain associated with a cutaneous SCC is thought to be a warning signal for invasive tumour and has been associated with an increased risk of overall mortality in these patients. Melanoma-related mortality was also reported to be 2-5 times higher in OTRs when compared with nonrecipients (Robbins et al., 2015). SCC and BCC tend to appear 8-10 years after OTRs undergo transplantation, specifically in sun-exposed regions of the skin (Ulrich et al., 2008).

IMPORTANT RISK FACTORS

Risk factors for skin cancer in OTR are similar to those in individuals with a healthy immune system, the most important of which are fair skin (Fitzpatrick skin types I-III), eyes and hair, as well as sun exposure. Sun exposure has a snowball effect in regards to skin cancer, as increased amounts of ultraviolet (UV) radiation exposure across one's life is one of the most significant carcinogens that causes skin cancer (Euvrard et al., 2003). UV B and A are present in ground level sunlight, however UVB is more readily absorbed by DNA leading to gene mutations, thus making it more carcinogenic than UVA (de Gruijl, 2000).

UV RADIATION EXPOSURE

Proving that sun exposure is one of the most important risk factors for skin cancer, NMSC lesions are ordinarily seen only on UV exposed skin areas. Furthermore, NMSC are more abundant in individuals living in countries with a sunnier climate. Therefore one of the most crucial factors that plays a role in decreasing the risk of skin cancer is sun protection (Euvrard et al., 2006).

With regards to UV radiation in OTRs, the severe carcinogenic effect of UV radiation plays an even greater role when compared to the general population. UV radiation itself causes both local and systemic immunosuppression (Yu et al., 2014), so when combining this with the lifelong immunosuppression treatment that OTRs need, these patients have a much higher risk for developing malignancies as their immune system is rendered almost ineffective to carry out tumour immune surveillance (Mittal & Colegio, 2017). It is therefore crucial for OTRs to receive sufficient education about sun protection and UV avoidance as much as possible.

AGE

Another important risk factor is age, as studies have shown that there is a higher prevalence of NMSC in older patients receiving transplants (Otley et al., 2005), as older patients have been exposed to UV for longer and have a waning immunity.

PREVIOUS SKIN CANCER, GENDER AND GENETIC POLYMORPHISMS

History of previous skin cancer, male sex and genetic polymorphisms are also risk factors for skin cancer in OTR. Mutations in the p53 tumour suppressor gene are the most common mutations found in skin cancers, thus making it a good marker to estimate cancer risk (Page et al., 2006). Tumour protein 53 (TP53) mutations allow tumour cells to withstand apoptosis and proliferate, while destroying healthy nearby keratinocytes. Other genes that are commonly mutated include cyclin kinase inhibitor 2A mutations (CDKN2A), Ras and NOTCH1 (Que et al., 2018). CDKN2A mutations affect the cell cycle by damaging the control proteins responsible for the cell cycle progression, differentiation, senescence and apoptosis (Brown et al., 2004). Ras mutations affect cellular signal transduction, and NOTCH1 mutations act as a rate-limiting step for carcinogenesis, most notably SCC (South et al., 2014).

UNDERLYING DISEASE

Specific underlying diseases were also shown to have an effect on skin cancer risk in OTRs. It was noted that there was an associated decreased skin cancer risk in kidney transplant recipients with underlying diabetes, however an increased skin cancer risk in kidney transplant recipients with underlying polycystic kidney disease (Kaufmann et al., 2005). When observing liver transplant recipients there was an associated increased skin cancer risk in patients with underlying cholestatic liver disease and cirrhosis (Otley et al., 2005).

HUMAN PAPILLOMAVIRUS

Immunosuppression also causes OTRs to be more vulnerable to viruses when compared to the general population, and this is of particular importance when considering Human papillomavirus (HPV) infections which are another risk factor for skin cancer (Mittal & Colegio, 2017). HPV is most notably associated with SCC, however does not seem to be linked with BCC. Cutaneous SCC was in fact thought to have originated both from DNA damage due to UV radiation as well as HPV exposure (Ally et al., 2013). In fact, studies showed that HPV DNA is found in 11-32% of normal skin, however is found in up to 90% of cutaneous SCCs in OTRs (Nindl et al., 2007).

In non-white transplant recipients, tumours are more often located in non-sun-exposed areas and are, in most cases, associated with HPV infection. Epstein-Barr virus (EBV), Hepatitis B virus (HBV), hepatitis C virus (HCV), Kaposi sarcoma herpes virus (KSHV), human T cell lymphotropic virus type 1 (HTLV-1), and Merkel cell polyomavirus (MCPyV) are other relevant viruses in this setting (Schiller & Lowy, 2021).

EFFECT OF IMMUNOSUPPRESSIVE DRUGS

OTRs also have an increased risk for malignancy due to the direct influence of the immunosuppressive treatment that the patient is on (Mittal & Colegio, 2017). Apart from the choice of immunosuppressive agent, the duration and intensity of treatment affects the development of consequent skin cancer (Bouwes et al., 1996). Exposure to immunosuppression has been shown to play a significant role, as studies show that a longer exposure has been associated with increased number of lesions (Euvrard et al., 2006). This is seen in heart transplant recipients who tend to have a twice as high risk for developing skin cancer when compared to renal transplant recipients (Wu & Orengo, 2002), due to the older age of such patients upon receiving the transplant, as well as due the more intensive immunosuppressant treatment that is necessary (Zwald & Brown, 2011).

Furthermore, certain specific immunosuppressive drugs also have direct carcinogenic actions along with their action on impairing the immune system. An example of such a drug is Azathioprine, as studies have suggested that Azathioprine exposure combined with UV exposure can lead to DNA damage which may in turn lead to malignancy (Jiyad et al., 2016; O'Donovan et al., 2005). Cyclosporine is another commonly used immunosuppressant drug, which has been reported to have potential adverse side effects leading to skin cancer (Muellenhoff & Koo, 2012).

However, newer immunosuppressive drugs such as Mycophenolate, Tacrolimus, Sirolimus and Everolimus have proven to be much less carcinogenic, implying a more hopeful outlook for OTRs, despite these drugs being much more expensive.

CONCLUSION

Skin cancer may be a very serious condition, and is significantly more likely to occur in OTRs who are on lifelong immunosuppressants. Not only are OTRs more likely to develop skin cancers, but such malignancies are more aggressive when compared to skin cancers in non transplant patients. Important risk factors for the development of skin cancer in OTRs include: skin type; UV radiation exposure (which is one of the most significant carcinogens in relation to skin cancer); older age; male gender; history of previous skin cancer; mutations such as TP53, Ras, CDKN2A and NOTCH1; underlying disease; HPV and other viruses such as EBV, HBV, HCV, KSHV, HTLV-1, and MCPyV; and the effects of the specific immunosuppressive drugs used. The importance of skin cancer prevention should be emphasised in OTRs especially due to their increased risk, and sufficient education should be delivered to such patients regarding sun protection and UV avoidance.

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