Merkel Cell Carcinoma and Immunosuppression: What We Still Need to Know

Frederick L. Locke, Dana E. Rollison, Vernon K. Sondak

The link between prolonged immunosuppression and nonmelanoma skin cancer (NMSC) is well established (1). Long-term immunosuppressive therapy is required after solid organ transplantation to prevent rejection and after allogeneic hematopoietic cell transplantation to prevent graft-versus-host disease (GVHD). Transplant patients are at increased risk for many cancers, with squamous cell carcinoma (SCC) and basal cell carcinoma (BCC) of the skin most common. Numerous factors contribute to this increased risk, including the type and duration of immunosuppressive therapy, cumulative amounts of sun exposure, and patient skin type and ethnicity. An association between Merkel cell carcinoma (MCC), a much rarer form of NMSC, and immunosuppression was recognized over two decades ago; however, the rarity of the disease limited the ability of early studies to tease apart independent risk factors for MCC (2).

In this issue of the Journal, Clarke et al. (3) leveraged the computer-based linkage of national transplant registries and population-based cancer registries to evaluate risk factors for MCC development among solid tumor transplant recipients within the Transplant Cancer Match Study (transplantmatch.cancer.gov). This study is important for several reasons. First, it provides a confident epidemiological association between immunosuppression and MCC, a cancer that is recognized to be associated with genomic integration of viral DNA (4). Second, it offers a more precise estimate of the increased relative risk of MCC development (approximately 24-fold over healthy control patients) in transplant recipients, an ideal population for research focused on prevention, causation, and treatment of MCC. Third, this study provides provocative but preliminary data on a possible synergistic link between sun exposure and certain immunosuppressive drugs that increase the likelihood of MCC development, supporting laboratory findings by others (5,6).

In 2008, it was discovered that DNA of a previously unidentified polyomavirus—now called the Merkel cell polyomavirus (MCPyV)—was integrated into the genome of the majority of MCC tumors (4). Clonal integration suggests that MCPyV is a contributing factor in MCC pathogenesis, with viral integration occurring before tumor clonal expansion. The mechanisms by which immunosuppression interacts with MCPyV to cause MCC remain unknown. It has long been postulated that immune dysregulation increases cancer development because of faulty immunoediting: Immune effectors that normally destroy aberrant clonal cells are unable to do so (7). An alternate mechanism is direct oncogenesis by infectious agents uncontrolled by an impaired immune response. This latter hypothesis is supported by a growing list of viruses associated with cancer development (human papillomaviruses [HPV], Epstein-Barr virus, human T-lymphotrophic virus-1, human herpesvirus 8, hepatitis B and C virus, and human immunodeficiency virus [HIV]), particularly among immunocompromised individuals (8). Our understanding of the role each of these viruses plays in the causation of cancers has evolved to include multiple mechanistic pathways.

In MCC, drug-induced immunosuppression likely facilitates replication of MCPyV, which, in turn, increases the chance of the virus integrating into the MCC progenitor cell, presumed to be the cutaneous Merkel cell. The synergism observed in this study between cyclosporine/azathioprine and ultraviolet (UV) exposure suggests that the drugs themselves may promote UV-associated DNA damage and/or inhibit DNA repair, increasing the risk of malignant transformation. Although this hypothesis is supported by mechanistic studies in the laboratory (5,6), the number of MCC case patients in the current study (110), even though drawn from 189 498 organ transplant recipients, is too small to allow confident conclusions about the relative carcinogenic risk of specific drugs or combinations.
A growing body of evidence suggests there also may be viral etiologies for BCC/SCC, with cutaneous HPV detected in SCCs from immunosuppressed patients (9–11). The cutaneous HPV oncoproteins have been shown to increase persistence of UV-induced DNA damage (12) and promote tumor growth (13). To better understand the effects of immunosuppression, viral infection, and UV exposure in relation to NMSC risk in transplant patients, additional studies are needed. These studies should incorporate biomarkers of viral infection both before and after transplant, as well as patient-level measurements of UV exposure, such as the difference between facultative and constitutive pigmentation as determined by spectrophotometry (14,15). Following transplant patients over time is more feasible than following most other populations, given the intensive medical surveillance they undergo. Skin cancer screening exams could be incorporated into their routine follow-up, providing an opportunity for better NMSC case ascertainment as well as early detection and intervention.

MCC is a rare cancer, yet there are important opportunities to improve patient outcomes in this and other NMSCs. Individuals with chronic lymphocytic leukemia and those infected with HIV are also at substantially increased risk for MCC (16,17) and, like transplant recipients, for NMSC as well. Importantly, immunosuppressed patients are at higher risk of developing metastatic disease from their NMSC (18). The enormous financial resources organ transplantation requires, along with the precious nature of donor organs, compounds the tragedy of losing a transplant patient to secondary cutaneous malignancy. Although there is no doubting the risk of NMSC is increased in organ transplant recipients, the exact magnitude of the burden is difficult to quantify because we have such poor data on skin cancer incidence rates in the general population and in immunosuppressed individuals. Given the substantial and growing costs associated with NMSC in this country (19), government funding for population-based cancer registries should support far more effective data collection for NMSC than is currently the case.

An important secondary issue raised by this study is the question of how, if at all, these data should be used to influence transplant physicians’ selection of immunosuppressive regimens for patients at risk of NMSC (eg, elderly patients with substantial chronic sun exposure and fair skin). Caution must be used because the evidence presented here does not convincingly implicate one or another drug as a causative agent. Numerous variables factor into the selection of transplant immunosuppression, such as practitioner familiarity, institutional and regional preference, differential effects on immune cell subsets, and expected toxicity profile in relation to patient comorbidities. Still, the data presented suggest that in recipients with a history of NMSCs, extensive sun exposure, and/or fair skin, alternatives to a cyclosporine/azathioprine combination should be considered when otherwise feasible.

Given recent successes of immune-based therapies against cancer, it is natural to consider such therapies for a cancer that is more common in immunosuppressed individuals. Immunotherapy for MCC could include immunomodulatory checkpoint antibodies, adoptive cellular therapies, or MCPyV vaccines or antiviral agents. Additional studies of immunomodulatory drugs such as ipilimumab and agents that block the PD-1/PD-L1 axis are urgently needed for patients with metastatic MCC, and are further supported by preliminary observations that improved survival was associated with increased localized inflammatory response and PD-L1 expression (20). Ipilimumab has been used safely in small series to treat cancer after transplantation (21,22); however, investigators should use caution, because antibodies that block T cell inhibitory signals may precipitate rejection of a solid organ or incite GVHD following allogeneic hematopoietic stem cell transplant (23). Cellular therapies, including tumor infiltrating lymphocytes and polyclonal antiviral epitope T cells, are under investigation in MCC (http://clinicaltrials.gov/show/NCT01758458) and as treatment for HPV-induced cancers (24,25).

Over 28,000 patients receive solid organ transplants yearly in the United States (http://optn.transplant.hrsa.gov/converge/data/), and an additional 7000 undergo allogeneic hematopoietic cell transplant (www.cibmtr.org). Transplant recipients require prolonged immunosuppressive medications and are at increased risk for NMSCs, including MCC. Considering recent scientific advances in understanding virus-associated cancers, the research community should intensify our focus on these high-risk populations. Increased attention to the selection of immunosuppressive medications, integrated risk-stratified dermatologic surveillance, procurement of stronger epidemiologic data regarding all NMSCs, and the pursuit of novel therapeutics for these cancers are likely to one day lead to improved patient outcomes—improving the survival rates and quality of life for transplant recipients while decreasing costs. Clearly, there is a lot more we need to know.

References


