NMSC in Organ Transplant Recipients and Other High-Risk Groups

Brent E. Pennington, MD, and Thomas Stasko, MD, Nashville, Tennessee

Key Words
NMSC, squamous cell carcinoma, organ transplant recipients, immunosuppression

Abstract
Non-melanoma skin cancers (NMSCs) are the most commonly occurring malignancies in the United States, with over 1 million cases being reported in 2002. These cases are primarily comprised of basal cell carcinomas (BCCs) and squamous cell carcinomas (SCCs) with a standardized ratio of BCC to SCC of 4:1. Within the general population, several subsets of patients are at particularly high risk for the development of these cutaneous malignancies. These groups include patients with lymphoproliferative disorders, basal cell nevus syndrome, xeroderma pigmentosum, epidermodysplasia verruciformis, and those receiving systemic immunosuppression. In addition to an increased incidence of NMSCs, these patients experience more aggressive neoplasms with a higher rate of associated metastatic disease. The largest and most well-documented subset of these patients are those who have undergone solid organ transplantation. According to the United Network for Organ Sharing, 24,893 solid organ transplantations were performed in 2002 in the United States.

Epidemiology of Skin Cancer in Organ Transplant Recipients
Organ transplant recipients have been found to have a three- to sevenfold increase in the incidence of post-transplantation cancers compared with the general population when all types of malignancies are considered. However, the risk of cutaneous SCC for transplant recipients has been reported to be as high as 250 times that of the general population. A retrospective review of heart and kidney transplant recipients of Norway from 1963 to 1992, with a median follow-up time of 4.8 years, found the incidence of cutaneous SCC to be 65 times that of the general population when controlled for age and gender. Increased risks were also seen for SCC of the lip (20-fold), Kaposi’s sarcoma (84-fold), and melanoma (20-fold). Similarly, a review of over 5000 patients undergoing solid organ transplantation in Sweden between 1970 and 1994 revealed a 100-fold increased incidence of SCC. Although less well documented in national cancer registries, the incidence of BCC in OTRs has been estimated to be 10 times that of the general population. The incidence of NMSC increases with the duration of immunosuppression. The prevalence of NMSC in renal transplant recipients of Queensland, Australia, was 7\% 1 year after transplantation, 45\% at 11 years, and 75\% at 20 years. In Australian heart transplant recipients,
prevalence rates of NMSC were 31% at 5 years and 43% at 10 years. In the United States, a cohort of heart transplant recipients exhibited a cumulative risk of NMSC of 3% at 1 year, 21% at 5 years, and 35% at 10 years following transplantation. In Dutch renal transplant patients, the prevalence of NMSC was 10% and 40% at 10 and 20 years after transplantation, respectively. These prevalence rates also demonstrate the increasing susceptibility of OTRs to the development of NMSC with increasing proximity to the equator.

The degree of immunosuppression also affects the rate of cutaneous carcinogenesis in organ transplant recipients (OTRs). Heart transplant recipients have a two- to fourfold higher incidence of SCC than renal transplant recipients when controlled for age and sex. This increased incidence is believed to be a reflection of the higher levels of immunosuppressive therapy required by heart transplant recipients. OTRs on triple therapy with prednisone, azathioprine, and cyclosporine have three to four times the incidence of SCC compared with those on prednisone and azathioprine alone. Renal transplant recipients receiving low-dose cyclosporine developed fewer NMSCs than those receiving high-dose cyclosporine.

NMSCs occurring in OTRs show a more aggressive biologic activity than those occurring in immunocompetent hosts. SCCs in renal transplant patients recurred locally in 84% of patients more than initial primary treatment. Rates of metastasis of SCCs range between 6% and 9%. Metastatic NMSC occurs rapidly after initial diagnosis, and it is a significant source of mortality in OTRs. In a review of 68 OTRs with metastatic skin cancer, the metastatic disease developed a mean of 1.4 years after diagnosis of the primary tumor. The three-year disease-specific survival of this group of patients was 54%. In a group of Australian heart transplant recipients, 27% of deaths occurring after the fourth year after transplantation were attributable to metastatic skin cancer when all types of skin cancer were considered. This significant degree of mortality attributable to skin cancer is corroborated by the data of the Cincinnati Tumor Registry, which showed that 5.2% of all transplant patients die from skin cancer and almost two-thirds of these skin cancers are SCCs.

**Etiology of NMSC in OTRs**

Numerous factors have been implicated in the development of NMSC in OTRs (Fig. 1). Ultraviolet (UV) radiation exposure has repeatedly been identified as the strongest predictive factor for the development of NMSC in transplant recipients as well as the general population. Ultraviolet radiation contributes to cutaneous carcinogenesis by two separate mechanisms. First, both UVA and UVB are capable of inducing signature mutations in cellular DNA. This occurs through the formation of DNA photoproducts via absorption of ultraviolet radiation. The most common ultraviolet photoproducts are cyclobutane pyrimidine dimers and 6-4 pyrimidine-pyrimidone dimers. Failure to remove these photoproducts by excision repair enzymes enables incorrect DNA transcription to take place at these sites, leading to single-base substitutions of thymine for cytosine and guanine for thymine after UVB and UVA exposure, respectively.

The accumulation of these UV-induced mutations in specific oncogenes or tumor-suppressor genes can lead to unrestricted cellular proliferation with subsequent malignancy formation. The most well-documented site for UV-induced mutations in SCCs and BCCs is the tumor-suppressor gene p53. The p53 gene product is responsible for a number of cellular functions, the most important of which is controlling the cellular response to DNA damage. Up-regulation of p53 in response to cellular DNA damage results in either arrest of the cell cycle in G1 or the initiation of programmed cell death, or apoptosis. Several studies showed approximately 50% of all SCCs and BCCs...
to contain mutations in p53. More recently, an increased susceptibility to the development of BCCs and SCCs was identified in renal transplant recipients possessing a certain common polymorphism of p53, but these results have not been substantiated by others.

In addition to this mutagenic ability, ultraviolet radiation exerts an immunosuppressive effect on the skin. UV-induced tumors in mice are rapidly rejected when transplanted into genetically identical nonirradiated mice; however, the administration of a subcarcinogenic dose of ultraviolet radiation before transplantation prevents this rejection and allows further tumor growth. Ultraviolet radiation also suppresses the contact hypersensitivity response in skin. Ninety percent of patients with a history of NMSC did not respond to the application of dinitrochlorobenzene to the forearm after initial sensitization on UV-irradiated buttock skin. The possible mechanisms by which this UV-induced immunosuppression of the skin takes place include a reduction in the antigen-presenting Langerhans cells within the dermis, a shift from a Th1 to a Th2 immunologic response, and the up-regulation of UV-induced soluble mediators such as tumor necrosis factor α, interleukin-10, and uro-canic acid. Although the relative importance of each of these mechanisms is debated, the cumulative effect of ultraviolet radiation on the skin is a reduction in tumor antigen presentation and recognition leading to enhanced tumor growth.

The immunosuppressive medications required to maintain transplanted organs are known to contribute to the development of NMSC (Table 1). Their role in cutaneous carcinogenesis appears to occur through two separate mechanisms. The profound suppression of the immune system produced by these agents results in impaired tumor antigen presentation. Neoplasms in these individuals are thus more likely to escape immune detection and continue to proliferate. Increased incidences of NMSC have been documented with the use of calcineurin inhibitors (cyclosporine A, tacrolimus) and anti-proliferative agents (azathioprine, mycophenolate mofetil). The effect of systemic steroids on tumorigenesis is less clear. Irradiated mice treated with prednisone showed no increase in cutaneous malignancies as opposed to those on cyclosporine or azathioprine. However, a retrospective case-control study revealed prior long-term systemic steroid use to be more common in non-transplant patients with NMSC than controls. No increased incidence of cutaneous malignancies has been associated with the use of sirolimus, OKT3, or antithymocyte globulin.

In addition to the enhanced carcinogenesis that occurs through impaired tumor surveillance, some of the immunosuppressive agents are directly carcinogenic. When administered to mice with severe combined immunodeficiency, cyclosporine induced cells to acquire an invasive phenotype and promoted tumor growth. This effect is believed to be caused by the up-regulation of transforming growth factor β by

<table>
<thead>
<tr>
<th>Drug</th>
<th>Mechanism of Action</th>
<th>Effect on NMSC</th>
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<tbody>
<tr>
<td>Antithymocyte Globulin</td>
<td>Rapid depletion of B and T lymphocytes by immune complex formation</td>
<td>None†</td>
</tr>
<tr>
<td>OKT3</td>
<td>Anti-CD3 humanized monoclonal antibody; Rapidly depletes T cells</td>
<td>None†</td>
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<tr>
<td>Cyclosporine A</td>
<td>Calcineurin inhibitor; decreases IL-2 and other cytokine production</td>
<td>Increased†</td>
</tr>
<tr>
<td>Tacrolimus</td>
<td>Calcineurin inhibitor; decreases IL-2 and other cytokine production</td>
<td>Increased†</td>
</tr>
<tr>
<td>Azathioprine</td>
<td>Inhibits purine synthesis</td>
<td>Increased†</td>
</tr>
<tr>
<td>Mycophenolate mofetil</td>
<td>Inhibits guanosine nucleotide synthesis</td>
<td>Increased†</td>
</tr>
<tr>
<td>Prednisone</td>
<td>Reduce lymphocyte proliferation through inhibition of macrophage production of IL-1, IL-2, IL-6, and other cytokines</td>
<td>Possible increase†</td>
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| Sirolimus                   | Inhibits mammalian target of rapamycin, which blocks IL-2-mediated signal transduction | Possible decrease†
cyclosporine. Similarly, azathioprine also has been shown to possess intrinsic carcinogenic effects. In contrast, sirolimus, an inhibitor of the mammalian target of rapamycin, has been shown to have significant antiproliferative activity against a broad range of human tumor cell lines.

A possible role for human papilloma virus (HPV) in the development of NMSCs in OTRs has been suggested. The increased incidence of cervical carcinoma in these patients and its association with HPV infection, particularly types 16 and 18, are well established. Numerous HPV types have been identified in benign and malignant cutaneous lesions of OTRs, and these types include those associated with epidermodysplasia verruciformis (HPV 5,8). Multiple HPV types are often identified within a single skin lesion. Studies have documented rates of HPV infection in tissue from SCCs of both OTRs and immunocompetent patients to be greater than 80%. Another study found equally high rates of HPV infection in hair follicles of renal transplant recipients regardless of their history of skin cancer.

The proposed mechanism by which HPV contributes to NMSC development involves the interaction between the HPV oncoprotein, E6, and the p53 gene product. E6 promotes ubiquitin-mediated degradation of the p53 protein, resulting in inhibition of apoptosis and continued cellular proliferation. The 72-codon arginine polymorphism of p53 is more susceptible to E6 degradation. The presence of this polymorphism in OTRs has been correlated with an increased incidence of NMSC in some, but not all studies examining the issue. The E6 oncoprotein is also capable of inhibiting apoptosis independent of p53 degradation.

Despite this apparent association between HPV infection and NMSCs in OTRs, several pieces of evidence against it also exist. First, equally high rates of HPV infection have been seen in benign cutaneous lesions of OTRs with and without a history of skin cancer. Also, the types of HPV identified in benign and malignant lesions are relatively similar, with no high-risk oncogenic type of HPV having been identified for cutaneous lesions. Thus, whether HPV infection plays a causative role in cutaneous carcinogenesis in OTRs or just represents an incidental cutaneous infection in an immunosuppressed population remains to be elucidated.

The relationship between human leukocyte antigens (HLA) and NMSC in OTRs also remains unclear. Initial studies indicated a negative association between HLA-A1 and NMSC in renal transplant patients and a positive association with HLA-DR7 and HLA-B27. However, multiple subsequent studies have failed to substantiate these associations. Thus, whether certain HLA antigens confer an increased susceptibility to cutaneous carcinogenesis in transplant patients has yet to be firmly established.

Prevention and Detection

All OTRs should undergo a skin focused history and physical before transplantation if possible. Although all OTRs on chronic immunosuppression are at increased risk for the development of skin cancer, certain risk factors predict a higher degree of susceptibility. History of a prior NMSC is a strong risk factor. In one cohort, 62% of patients with a history of NMSC before transplantation developed another skin cancer after transplantation. Some evidence also suggests that patients with a history of NMSC before transplantation are at greater risk for experiencing metastatic disease after transplantation.

Other factors portending an increased risk of NMSC are fair skin (Fitzpatrick types I-III) and a history of extensive sun exposure. Older age at transplantation has been correlated with an increased incidence of NMSC. As an exception, pediatric transplant patients appear to have a particularly high rate of skin cancer and associated metastatic disease.
Both the duration and the intensity of immunosuppression strongly affect the risk of skin cancer after transplantation.\textsuperscript{12,14,15} A low CD4 count has been identified also as a risk factor for NMSC in OTRs.\textsuperscript{65} Although reports in the literature regarding the possible pathogenesis of human papilloma virus in the development of skin cancer are conflicting, the history and physical should screen for the presence of warts.\textsuperscript{46–49} The physical examination should focus on the detection of warts, cutaneous horns, actinic keratoses, BCCs, and SCCs.

After a cutaneous malignancy has been identified, the physical examination should place particular emphasis on palpation for lymphadenopathy and detection of in-transit metastatic disease. Patients with evidence of local satellite lesions should receive an appropriate evaluation to exclude the presence of distant metastases. Mohs micrographic surgery or excision with margin control is indicated for resection of satellite lesions associated with a primary tumor.\textsuperscript{70} If this technique is not available, standard excision with margins of at least 1 cm is recommended.\textsuperscript{71} Adjunctive radiation therapy should be considered in all cases of satellite lesions. Alternatively, primary radiation therapy may be considered. The possibility of a reduction in immunosuppression should be discussed with the transplant physician.\textsuperscript{72}

All OTRs with high-risk SCCs who are found to have palpable lymphadenopathy should be referred for fine needle aspiration or excisional biopsy of the involved node. Patients with regional nodal involvement should be considered for local excision of the primary tumor with lymphadenectomy and adjunctive radiation therapy. All patients with distant or nodal metastases should be considered for retinoid chemoprophylaxis and possible reduction of immunosuppressive therapy.

All OTRs should receive intensive education regarding the performance of monthly skin self-examinations and the pathogenic role of sun exposure in cutaneous carcinogenesis. Emphasis must be placed on limiting the amount of sun exposure, wearing sun-protective clothing, and daily application of broad-spectrum sunscreens blocking UVA and UVB rays.\textsuperscript{71}

Current education efforts have been shown to be marginally effective in communicating the importance of these protective measures to transplant patients. Only 40% of renal transplant patients reported using sunscreen on a regular basis, and over 50% were unable to recall any education about sun protection at the time of transplantation.\textsuperscript{74} Less than 1 in 5 renal transplant recipients from another study reported being seen by a dermatologist annually.\textsuperscript{75} One potential solution to improving care and education in centers with large cohorts of transplant patients is the establishment of a multidisciplinary clinic staffed by dermatologists and transplant physicians. This has been done at the Mayo Clinic in an effort to provide intensive education on sun protection and to identify patients with strong risk factors for NMSC development early in their course.\textsuperscript{76}

In fair-skinned transplant patients, consideration can be given to the nightly application of a topical retinoid to sun-exposed areas.\textsuperscript{77,78} Chemoprophylaxis with systemic retinoids (acitretin,\textsuperscript{79–81} etretinate,\textsuperscript{78,82} and isotretinoin\textsuperscript{83,84}) may be considered in OTRs developing multiple NMSCs each year. Multiple studies have validated the efficacy of systemic retinoids in reducing the incidence of NMSCs in transplant recipients; however, this deceleration in cutaneous carcinogenesis is not maintained after the discontinuation of the retinoid. After retinoid withdrawal, most patients form cutaneous malignancies at a rate equaling or even surpassing the rate before therapy. Long-term studies assessing the effect of systemic retinoids on organ rejection are not available. As with all patients on systemic retinoids, contraception is essential in women of childbearing potential, and periodic monitoring of hepatic and lipid profiles is recommended.

**Clinical and Histologic Features of NMSC in OTRs**

As in immunocompetent individuals, the classical clinical appearance of a BCC in OTRs is that of a pearly papule or plaque with overlying telangiectasia and rolled borders. It may have the associated features of ulceration or pigmentation. SCCs typically present as a firm, flesh-colored to erythematous hyperkeratotic papule or plaque. It may have associated features of ulceration, an overlying cutaneous horn, or a verrucous appearance. OTRs often develop numerous lesions, and these SCCs frequently show aggressive growth with invasion of critical underlying anatomic structures (Figs. 2 and 3).

Given the pathogenic role of ultraviolet radiation in their development, both BCCs and SCCs will have a predilection for occurring on chronically sun-exposed areas. However, in contrast to immunocompetent
individuals, OTRs acquire the majority of their cutaneous malignancies on the dorsal forearms and hands rather than the face. Thus, the typical 9:1 ratio of NMSC on the face versus extremities is 1:4 in transplant recipients. Many transplant patients develop an almost confluent distribution of malignant and premalignant lesions on the dorsal hands and forearms, and this clinical entity has been given the name “transplant hand” (Fig. 4). Due to the widespread nature of dysplasia, this condition has often been treated with complete excision of the skin of the dorsal hand followed by split-thickness skin grafting.

The histopathology of nonmelanoma skin cancers in OTRs is similar to that in immunocompetent patients. SCCs typically show nests of squamous epithelial cells with abundant eosinophilic cytoplasm extending from the epidermis into the dermis. The cells show enlarged, vesicular-appearing nuclei with variable mitotic figures (Fig. 5). BCCs exhibit nests of basaloid cells with hyperchromatic nuclei extending into the dermis. Peripheral palisading of cells and surrounding stromal retraction are characteristic features. Great variability is seen in the histologic appearance of BCCs and multiple subtypes (that is, superficial, nodular, sclerosing, infiltrative, and pigmented) have been described. Features indicative of more-aggressive neoplasms include poor differentiation, perineural invasion, and extension into the subcutaneous fat. Although certain histologic features have been reported to occur more frequently in NMSC in transplant patients, cutaneous neoplasms arising in OTRs cannot consistently be distinguished from those in immunocompetent patients.

Other Groups at High Risk for Developing NMSC

Xeroderma pigmentosum (XP) is a heritable disorder resulting from impaired DNA-repair mechanisms. Patients can be divided into seven complementation groups based on specific defects in DNA excision repair. The cutaneous manifestations of this disease include pain and erythema with minimal sun exposure, onset of freckling in sun-exposed regions in infancy,
and the early development of cutaneous malignancies. The median age for first NMSC in XP patients is eight years. They have a 1000-fold increased risk for the development of BCCs, SCCs, and melanoma. XP patients also frequently have ocular abnormalities such as photophobia and corneal opacification. Approximately 30% of patients exhibit neurologic abnormalities of variable severity. Management of XP patients centers on early diagnosis followed by the institution of strict lifelong protection of the skin and eyes from UV radiation with topical sunscreens and UV-protective clothing and glasses. Patients should be educated in the performance of monthly self-examinations and be followed up regularly by a dermatologist for the early detection and treatment of neoplasms. The treatment of skin cancers in XP patients does not differ except in the fact that caution should be used with radiation therapy because some complementation groups are hypersensitive to its effects. For XP patients with multiple malignancies, consideration should be given to chemoprophylaxis with acitretin because this has been shown to reduce the rate of cutaneous carcinogenesis.

Basal cell nevus syndrome (BCNS), or Gorlin’s syndrome, is an autosomal dominant condition characterized by the development of multiple BCCs, pits on the palms and soles, cysts of the jaw, bifid ribs, and calcification of the falx cerebri. It is the result of a mutation on chromosome 9 in the PATCHED1 gene, whose protein product participates in the sonic hedgehog signaling pathway. BCCs in BCNS patients cannot be distinguished clinically from their counterparts in normal hosts. What is striking is that these lesions occur at a relatively young age and in unusual sites. This suggests that some aspect of the hedgehog signaling pathway may be dysregulated in these patients. Given the widespread occurrence of BCCs, topical application of either 5-fluorouracil cream or imiquimod cream may be tried for superficial BCCs. Radiation therapy should not be employed in BCNS patients because it has been reported to enhance cutaneous carcinogenesis in the radiation field. Chemoprophylaxis with systemic retinoids has been reported to benefit BCNS patients also, but the use in BCNS is less well documented than in organ transplantation or XP.

Epidermodysplasia verruciformis is a disorder in which affected individuals display an increased susceptibility to human papilloma virus (HPV)-induced warts. The majority of cases are inherited in an autosomal recessive manner, but instances of X-linked transmission and spontaneous mutation have been reported. The cutaneous lesions typically appear as flat-topped flesh-colored common flat warts or as scaling red-brown macules resembling pityriasis rosea or tinea versicolor. These red-brown macules are associated with EV-specific HPV types, the most notable being HPV 5 and 8. More than half of EV patients followed up for 30 years display malignant transformation of warts into SCC. The development of this malignant disease usually begins in the fourth or fifth decade and occurs almost exclusively in sun-exposed areas of the face, forearms, and upper back. Treatment centers on protection of the skin from UV radiation. Traditional surgical methods should be used for cutaneous SCCs. The use of radiation therapy should be limited in EV patients because of the possibility of enhanced carcinogenesis. Therapy with cimetidine and the combination of acitretin and interferon alfa-2a were reported in individual case reports to have resulted in decreased cutaneous wart formation in EV patients.

Patients with chronic lymphocytic leukemia have an increased incidence of secondary malignancies including NMSC. Retrospective analyses indicate a four- to eightfold increase in the development of NMSCs in this population. SCCs in CLL patients as compared with those in normal patients appear more aggressive histologically and are associated with higher rates of metastatic disease. Appropriate management centers on ultraviolet protection of the skin along with frequent surveillance for new tumor formation.

Conclusions

NMSC represents the most frequently occurring malignancy in the United States. Patients with xeroderma pigmentosum, basal cell nevus syndrome, epidermodysplasia verruciformis, chronic lymphocytic leukemia, and solid organ transplants are at particularly high risk for the development of these malignancies. Of these, organ transplant recipients comprise...
the largest and most well documented group. The approach to the management of NMSC in transplant patients provides insight into the etiology, diagnosis, treatment and prevention of cutaneous neoplasms in these other high-risk patients.

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