Decreased Skin Cancer After Cessation of Therapy With Transplant-Associated Immunosuppressants

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Background: Immunosuppression for solid organ transplantation is associated with increased incidence of internal and cutaneous malignant tumors, among which skin cancer is the most common.

Objective: To determine the effects on cutaneous carcinogenesis when stopping therapy with immunosuppressive medications.

Observations: We followed the clinical course of 6 solid organ transplant recipients after therapy with immunosuppressant medications was stopped because of allograft failure or unacceptable cutaneous carcinogenesis. Generally, we found that stopping therapy with immunosuppressive medications resulted in deceleration of cutaneous carcinogenesis, resolution of cutaneous verrucae vulgaris, and qualitative improvements in skin condition. Four patients experienced marked improvement; 2 did not.

Conclusions: Cessation of transplant-associated therapy with immunosuppressive medications for patients in whom cutaneous carcinomas developed after transplantation may lead to deceleration of cutaneous carcinogenesis, decreased verrucae, and improved skin quality within 1 to 2 years. Because of the natural variation in skin cancer development and the small number of cases in this series, definitive conclusions require further study.

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RESULTS

We observed 6 solid organ transplant recipients who had a history of cutaneous carcinomas. After therapy with immunosuppressant medications was stopped, cutaneous carcinogenesis decelerated and skin quality improved for 4 of the patients.

Immunosuppression is essential for approximately 21,000 transplant recipients in the United States each year. Intense immunosuppression with multiantigent regimens is necessary to prevent allograft rejection. Unfortunately, immunosuppressive regimens have nonspecific effects, causing a profound and nonspecific dysfunction of humoral and cellular immunity. An unintended consequence of immunosuppression is that internal and cutaneous malignancies occur at a markedly increased rate in transplant recipients. In fact, skin cancer is the most common posttransplantation malignancy.

For many transplant recipients, skin cancer is a minor, easily managed problem. However, some transplant recipients experience explosive, potentially life-threatening cutaneous carcinogenesis. Occasionally, therapy with immunosuppressive medications must be discontinued (with resultant graft failure) to prevent the progression of potentially lethal skin cancers. Also, therapy with immunosuppressant medications may be discontinued after primary allograft failure. The effect of stopping the medicinal therapy on the course of cutaneous carcinoma formation in patients with a history of skin cancer is not well established. A report of liver allograft recipients who were weaned from immunosuppressant medications mentioned improvement of skin cancer for 1 of 2 patients. We describe the natural history of cutaneous carcinogenesis after therapy with immunosuppressant medications was discontinued in a cohort of 6 transplant recipients.

The clinical course of cutaneous carcinogenesis after discontinuing therapy with immunosuppressant medications in solid organ transplant recipients is depicted in Figures 1, 2, 3, 4, 5, and 6. The specifics of the clinical course of each pa-
PATIENTS AND METHODS

The clinical course of 6 solid organ transplant recipients was observed after discontinuation of therapy with immunosuppressant medications. The clinical features of these patients are listed in the Table. Patients were evaluated on a regular basis (usually every 2 to 6 months) with complete cutaneous and nodal examination. Biopsies were performed on clinically apparent skin cancers, and the cancers were managed with standard techniques, including electrodesiccation and curettage, curettage and cryotherapy, surgical excision, and Mohs micrographic surgery. Immunosuppressive medications were managed by the transplant physicians and were titrated to the lowest dose necessary to prevent allograft rejection. Standard therapeutic modalities, including cryosurgery, fluorouracil cream, and topical retinoids, were used to lessen the development of cutaneous carcinomas.

Cutaneous carcinogenesis, verrucae, and cutaneous quality were monitored after therapy with immunosuppressive medications was discontinued. The total tumor count per year was graphed for comparison among years for each patient. After a first allograft failed and therapy with immunosuppressive medications was discontinued for 9 months, patient 3 received a second transplant and the course of these same variables was monitored after retransplantation.

A 57-year-old man had received a kidney allograft in 1977 and experienced allograft failure in May 1999 (Figure 1). His cutaneous carcinomas, all of which were squamous cell carcinomas except for 2 basal cell carcinomas diagnosed in 1993, were manageable until their progression accelerated in 1997. The number of squamous cell carcinomas increased greatly in 1998 to a total of 45 tumors. During the first 3 months of 1999, allograft failure occurred and therapy with immunosuppressive medications was discontinued. Since the cessation of therapy with immunosuppressive medications in May 1999, the rate of cutaneous carcinogenesis has abruptly decreased, with the last skin cancers occurring in September 1999. Also noted was improvement in the roughness of the patient’s skin and a partial remission of cutaneous warts. The patient is receiving hemodialysis treatment and has no active malignancy.

PATIENT 2

A 28-year-old woman received a pancreas transplant in 1992. In August 1997, she experienced allograft failure and resumed insulin administration to control her insulin-dependent diabetes mellitus (Figure 2). Multiple squamous cell carcinomas developed in each year from 1995 to 1997; the last developed in February 1997. Her skin was extremely photo-damaged, with numerous actinic keratoses and lentigines, and she had extensive cutaneous warts. After therapy with immunosuppressant medications was discontinued in August 1997, only 2 small basal cell carcinomas appeared in early 1998. There have been no subsequent squamous cell carcinomas for 17 months. Additionally, there has been a dramatic clinical reversal of the photo-damage of her skin, including diminution of the actinic keratoses and lentigines. Plantar warts, which had been a frequent problem for this patient, resolved completely with several pulsed-dye laser treatments after discontinuing therapy with immunosuppressant medications. The patient has no active malignancy.

PATIENT 3

A 58-year-old man had received a kidney transplant in 1985 and experienced allograft failure in April 1998 (Figure 3). He had 1 squamous cell carcinoma in 1996 and another in 1997. Cutaneous carcinogenesis accelerated in early 1998 with 5 squamous cell carcinomas occurring before allograft failure. The patient was not receiving immunosuppressant medications between April 1998 and January 1999 when he successfully received a second kidney allograft and resumed immunosuppressant therapy. During the 9 months he was not receiving immunosuppressant medications, no new cutaneous carcinomas developed and all cutaneous warts resolved. However, since January 1999, 3 squamous cell carcinomas developed over 11 months. Additionally, approximately 30 warts and multiple actinic keratoses developed. The patient is being observed closely for skin cancer.

PATIENT 4

A 44-year-old man had received a kidney transplant in 1981 and experienced extensive cutaneous carcinoma development beginning in 1987 (Figure 4). In 1988, he had split-thickness skin graft repair of the entire dorsal surface of his right hand owing to extensive carcinoma formation. In 1995, the procedure was performed on his left hand. In 1991, he had metastatic squamous cell carcinoma in the left axillary lymph nodes that was managed with lymphadenectomy with no recurrence. In 1998, he had many cutaneous carcinomas, including a life-threatening, deeply invasive squamous cell carcinoma of the scalp. In December 1998, a decision was made to discontinue therapy with immunosuppressive medications and allow allograft rejection because of
### Clinical Characteristics of Study Patients

<table>
<thead>
<tr>
<th>Patient No./ Sex/ Age, y</th>
<th>Transplanted Organ</th>
<th>Reason for Cessation of Medicinal Therapy</th>
<th>Immunosuppressant Medications</th>
<th>Other Malignancies</th>
<th>Effect of Cessation of Therapy With Immunosuppressant Medications</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/M/57</td>
<td>Kidney</td>
<td>Allograft failure</td>
<td>Azathioprine, prednisone</td>
<td>None</td>
<td>Probable decreased carcinoma formation; improved skin quality</td>
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<tr>
<td>2/F/28</td>
<td>Pancreas</td>
<td>Allograft failure</td>
<td>Tacrolimus, azathioprine, prednisone</td>
<td>Thyroid carcinoma in remission</td>
<td>Decreased carcinoma formation; resolution of warts; improved skin quality</td>
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<td>3/M/58</td>
<td>Kidney</td>
<td>Allograft failure</td>
<td>Azathioprine, prednisone</td>
<td>None</td>
<td>Temporary decreased carcinoma formation and resolution of warts, followed by recurrence of carcinoma formation and warts after retransplantation</td>
</tr>
<tr>
<td>4/M/44</td>
<td>Kidney</td>
<td>Uncontrolled skin cancer</td>
<td>Azathioprine, prednisone</td>
<td>History of monoclonal gammopathy</td>
<td>No decrease in carcinoma formation; no recurrence of metastatic squamous cell carcinoma</td>
</tr>
<tr>
<td>5/M/42</td>
<td>Kidney</td>
<td>Allograft failure</td>
<td>Azathioprine, prednisone, cyclosporine (1988-1992)</td>
<td>None</td>
<td>Decreased carcinoma formation and decreased actinic keratosis; died of pancreatic cancer</td>
</tr>
<tr>
<td>6/M/55</td>
<td>Kidney</td>
<td>Allograft failure</td>
<td>Azathioprine, prednisone</td>
<td>None</td>
<td>Decreased carcinoma formation and decreased actinic keratosis; died of pancreatic cancer</td>
</tr>
</tbody>
</table>

**Figure 1.** Patient 1. Skin cancer course of a 57-year-old man who had undergone kidney transplantation in 1977 and allograft failure in May 1999. Therapy with immunosuppressive medications was stopped in May 1999. The last skin cancers developed in September 1999. NMSCs indicates nonmelanoma skin cancers.

**Figure 2.** Patient 2. Skin cancer course of a 28-year-old woman who had undergone pancreas transplantation in 1992 and allograft failure in August 1997. Therapy with immunosuppressive medications was stopped in August 1997. NMSCs indicates nonmelanoma skin cancers.

**Figure 3.** Patient 3. Skin cancer course of a 58-year-old man who had undergone kidney transplantation in 1985, allograft failure in April 1998, and retransplantation in January 1999. Therapy with immunosuppressive medications was stopped from April 1998 to January 1999. NMSCs indicates nonmelanoma skin cancers.

**Figure 4.** Patient 4. Skin cancer course of a 44-year-old man who had undergone kidney transplantation in 1981. Therapy with immunosuppressive medications was stopped in December 1998. NMSCs indicates nonmelanoma skin cancers.
concern for potentially lethal cutaneous malignancies. Since then, he has continued to develop many cutaneous carcinomas, including 47 in 1999. Subjectively, there has been a mild improvement in his skin quality, and there may be an early trend toward deceleration of his cutaneous carcinogenesis. The patient is being observed closely for skin cancer.

**PATIENT 5**

A 42-year-old man had received a kidney transplant in 1984 and experienced allograft failure in February 1998 (Figure 5). The patient received cyclosporine from 1988 through 1992 in addition to his baseline regimen of azathioprine and prednisone. After developing 2 squamous cell carcinomas in 1993, he received isotretinoin (10 mg daily). All of his malignancies, except for 1 basal cell carcinoma in 1996 and 1 in 1998, have been squamous cell carcinomas. Because of extensive carcinoma formation, the patient had split-thickness skin graft repair of the dorsal skin on his left hand in 1995 and on his right hand in 1996. Isotretinoin was replaced with etretinate (25 mg daily) for his treatment regimen in May 1995. The dosage of etretinate was increased to 50 mg daily in November 1995. Subsequently, etretinate was replaced with isotretinoin (40 mg daily) in June 1997. Therapy with isotretinoin was discontinued in October 1997. Kidney allograft failure occurred in October 1997, and all therapies with immunosuppressant medications were stopped by February 1998. In 1998, he had 28 nonmelanoma skin cancers. In 1999, his cutaneous carcinogenesis decreased to a total of 14 nonmelanoma skin cancers. The patient is being observed closely for skin cancer.

**PATIENT 6**

A 55-year-old man had received a kidney transplant in 1993 and experienced allograft failure in February 1999 (Figure 6). A substantial number of skin cancers developed in 1997 and 1998: 41 (13 squamous cell carcinomas and 28 basal cell carcinomas) and 17 (10 squamous cell carcinomas and 7 basal cell carcinomas), respectively. In January 1999, before allograft failure, 25 skin cancers developed (19 squamous cell carcinomas and 6 basal cell carcinomas). After the discontinuation of therapy with immunosuppressant medications in February 1999, only 1 squamous cell carcinoma developed. In addition, the patient had a marked diminution of actinic keratoses. He died of metastatic pancreatic cancer in August 1999.

**COMMENT**

Profound immunosuppression is necessary for organ transplantation. Only with intense suppression of the immune system can allograft rejection be avoided. This profound immunosuppression is nonspecific, resulting in multiple, potentially adverse effects, including malignancy. Cutaneous carcinomas are the most common type of posttransplantation malignancy and range in severity from mild to life-threatening.1-4

Two mechanisms have been proposed for the accelerated carcinogenesis associated with immunosuppression: decreased immune surveillance resulting in uncontrolled proliferation of abnormal cells and the direct carcinogenic effect of medications, including azathioprine and cyclosporine. Ideally, immunosuppression would be selective for immune effectors involved in recognition of specific allograft antigens without causing generalized immunosuppression. Selective immunosuppression, however, remains elusive. Dantal and colleagues6 demonstrated that the development of internal and cutaneous malignancies can be reduced by decreasing the overall level of immunosuppression, albeit at the risk of having more rejection episodes. However, the effect of completely discontinuing therapy with immunosuppressant medications in patients who have had cutaneous carcinomas is not well established.5

Presumably, with the discontinuation of therapy with systemic immunosuppressive medications, complete restoration of humoral and cellular immunity would lead not only to the complete rejection of the allograft but also to enhanced immune surveillance and eradication of atypical or cancerous cells. In some cases when immunosuppressive therapy has been stopped, malignant tumors inadvertently transplanted with a donor organ have been eradicated.7 Additionally, the discontinuation of both cyclosporine and azathioprine therapy along with their po-
tential carcinogenic effects may be instrumental in reducing cancer formation.

Overall, our patients had decelerated development of cutaneous carcinomas, remission of warts, and subjective improvement in skin quality after the discontinuation of therapy with immunosuppressive medications. Four of 6 patients experienced notable improvement in all variables soon after therapy with immunosuppressive medications was stopped. We acknowledge that skin cancer rates can vary considerably after transplantation and that definitive conclusions require a larger study.

Interestingly, patient 3 underwent retransplantation 9 months after discontinuing his initial therapy with immunosuppressant medications. During the 9 months without the administration of immunosuppressant medications, no cutaneous carcinomas developed and all his warts resolved. This outcome argues strongly that improvement is related to stopping immunosuppressant therapy. Subsequent to resumption of immunosuppressant therapy, the recurrence of squamous cell carcinomas and warts suggests a causal effect.

For patients 4 and 5, the rate of cutaneous carcinoma development did not appreciably decrease during follow-up periods of 13 and 23 months, respectively. The course of patient 5 was confounded by the concomitant follow-up periods of 13 and 23 months, respectively. The course of patient 5 was confounded by the concomitant cessation of retinoid therapy shortly before the cessation of systemic immunosuppressant medications. The rebound of cutaneous carcinomas after the cessation of systemic retinoid therapy is well recognized. This effect may account for the numerous cutaneous carcinomas this patient experienced in the year after stopping therapy with immunosuppressant medications. In 1999, patient 5 experienced fewer cutaneous carcinomas, although the relationships among the multiple confounding factors remain unclear.

Patient 4 (the patient with the most cutaneous carcinomas) experienced a slight decrease in cutaneous carcinoma formation only recently and experienced more skin cancers in the year after stopping immunosuppressant therapy than at any other time. However, there has been no recurrence of 2 high-risk squamous cell carcinomas, including a squamous cell carcinoma that metastasized to the left axilla in 1991 and a large invasive squamous cell carcinoma of the scalp that was treated in 1998. Further follow-up may be necessary to ascertain the effects of stopping therapy with immunosuppressant medications in patients 4 and 5.

In summary, transplant recipients with a history of skin cancer may experience a deceleration of cutaneous carcinogenesis after the cessation of therapy with immunosuppressive medications. Additionally, cutaneous papillomavirus infections and overall cutaneous quality may improve with the discontinuation of therapy with immunosuppressant drugs. Although a small percentage of long-term allografts may survive despite the cessation of all therapies with immunosuppressant medications, the typical result is allograft rejection and end-stage organ failure. However, for uncontrollable cutaneous carcinogenesis or metastatic malignancy in patients with kidney or pancreas transplants, the cessation of all therapies with immunosuppressant medications may be warranted. These patients have the option of resuming hemodialysis or insulin therapy after allograft failure. Whereas survival without immunosuppressant therapy may be possible for 25% of long-term liver allograft recipients, survival of heart allograft recipients after the cessation of medicinal therapy has little documentation.

The decision-making process is complex for weighing the risks and benefits of stopping therapy with immunosuppressant medications and having subsequent graft failure against developing life-threatening skin cancer. However, the deceleration of carcinogenesis after stopping therapy with immunosuppressant medications is encouraging in these 6 patients, 5 of whom have continued to survive with replacement hemodialysis, insulin therapy, or retransplantation.

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REFERENCES