

REVIEW ARTICLE

MEDICAL PROGRESS

Skin Cancers after Organ Transplantation

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LONG-TERM SURVIVAL AFTER ORGAN TRANSPLANTATION IS INCREASING. As a result, many physicians may encounter patients who have long-term complications of transplantation. Adequate graft function requires lifelong immunosuppressive treatment, and the resultant modification of the immune system is associated with an increased risk of various cancers, particularly those involving viruses. Skin cancers are the most common malignant conditions in transplant recipients¹⁻⁴ (Table 1) and account for substantial morbidity and mortality in such patients. In this review, we discuss the most common forms of skin cancer in transplant recipients.

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SKIN CARCINOMAS

Squamous-cell and basal-cell carcinomas account for more than 90 percent of all skin cancers in transplant recipients.^{1,3,5,6} The incidence of these carcinomas increases with the duration of immunosuppressive therapy, ultimately affecting 50 percent or more of white transplant recipients.^{1,5,7} For example, the cumulative incidence of skin cancer in transplant recipients in Queensland, Australia, increases from 7 percent after 1 year of immunosuppressive therapy⁵ to 82 percent after 20 years.⁸ Among Dutch transplant recipients, the incidence of skin cancer at one year is 0.2 percent and the long-term incidence is 41 percent.⁵ Squamous-cell carcinoma is the most common skin cancer in transplant recipients, occurring 65 to 250 times as frequently as in the general population.^{6,7,9} The incidence of basal-cell carcinomas is reportedly increased by a factor of 10 in transplant recipients.⁷ The risk appears to increase linearly for basal-cell carcinomas and exponentially for squamous-cell carcinomas¹; thus, the ratio of squamous-cell to basal-cell carcinomas in patients without transplants (1:4) is reversed in transplant recipients.^{1,5,10} The relative risk of squamous-cell carcinoma after transplantation is higher for men than for women, except for cancers of the lip.⁹ Curiously, skin cancers appear to be extremely rare in Japanese patients with transplants.¹¹

The mean interval between transplantation and diagnosis of a tumor is eight years for patients who received transplants at approximately 40 years of age,¹⁰ but is only about three years for those who received transplants after the age of 60.¹ The severity of these tumors is linked to their number. Approximately 30 to 50 percent of patients with squamous-cell carcinomas also have basal-cell carcinomas.^{5,10} According to a Scandinavian study, 25 percent of patients with a first squamous-cell carcinoma will have a second lesion within 13 months, and 50 percent will have a second lesion within 3.5 years.⁹ Liddington et al. reported a mean interval of 15 months between detection of the first and second cancers, and 11 months between the second and third.¹²

Carcinomas are usually associated with multiple warts and premalignant keratoses, and are often associated with Bowen's disease (an intraepidermal carcinoma of the skin or mucous membranes that may progress to invasive carcinoma) and keratoacanthomas (Fig. 1A). The appearance of a lesion may be misleading; for example, lesions that look like warts may prove on histologic examination to be keratoacanthomas, Bowen's dis-

Table 1. Skin Tumors in Transplant Recipients and Cells of Origin.

Tumor Type	Cell of Origin
Basal-cell and squamous-cell carcinoma, actinic keratosis, Bowen's disease	Epidermal and hair-follicle keratinocytes
Melanoma	Melanocytes, nevus cells
Kaposi's sarcoma, angiosarcoma	Endothelial cells
Neuroendocrine skin carcinoma	Neuroendocrine (Merkel) cells
Lymphoma	B and T lymphocytes
Malignant fibrous histiocytoma	Histiocytic or fibroblastic cells

ease, or squamous-cell carcinomas. It is not always possible to distinguish between squamous-cell carcinoma and keratoacanthoma, even after histologic examination.^{12,13} Thus, keratoacanthoma in a transplant recipient should be considered equivalent to a squamous-cell carcinoma. Over time, several dozen tumors may develop in some transplant recipients, primarily in areas exposed to the sun. The distribution appears to be age-related: among patients who were under the age of 40 years at the time of transplantation, 80 percent of lesions are located on the dorsum of the hands (Fig. 1B), the forearms, or the upper trunk, whereas among older transplant recipients, 80 percent of lesions develop on the head.¹⁰

Squamous-cell carcinomas appear to be more aggressive in transplant recipients than in nonimmunosuppressed persons.¹⁴⁻¹⁷ Such tumors often grow rapidly. They recur locally in 13.4 percent of patients,³ generally during the first six months after excision, and metastasize in 5 to 8 percent of patients, usually during the second year after excision (Fig. 1C).¹⁸ An unfavorable prognosis is associated with the presence of multiple tumors,^{5,14,15} a cephalic location,¹⁴⁻¹⁶ the presence of extracutaneous tumors,¹⁵ older age,¹⁴ and — in our experience — high exposure to sun (e.g., in outdoor workers). However, metastases occur even in patients who underwent transplantation in childhood.^{19,20} Histologic features of aggressive tumors include poor differentiation,¹⁷ a tumor thickness of more than 5 mm, and invasion of underlying tissue (hypodermis, nerves, cartilage, muscle, and bone).¹⁴

RISK FACTORS

The pathogenesis of skin carcinoma is multifactorial, with extrinsic and intrinsic factors (Fig. 2). Ultraviolet radiation appears to be the most important factor, since the highest incidence of skin carcinomas is in countries with high sun exposure (e.g., Australia),⁵ and the tumors tend to develop in sun-exposed areas and in transplant recipients with a history of high sun exposure after (or even before) transplantation.^{21,22} Transplant recipients with fair skin are at much higher risk for the development of skin carcinoma than are those with dark skin.²² Ultraviolet radiation induces mutations in the p53 tumor-suppressor gene²³ and local immunodeficiency, as a result of a decrease in the density of epidermal Langerhans' cells.

The incidence of skin cancer is proportional to the level of immunosuppression.⁵ CD4 counts are significantly lower in transplant recipients with cutaneous carcinomas than in those without such lesions.²⁴ Rejection episodes in the first year after transplantation may predict patients at greater risk for skin cancer, possibly because they require higher levels of immunosuppressive treatment.²⁵ A retrospective study showed that kidney-transplant recipients who were receiving prednisolone, azathioprine, and cyclosporine had a risk of squamous-cell carcinoma that was three times as high as the risk among those receiving prednisolone and azathioprine alone.⁶ A five-year randomized, prospective study showed that low-dose cyclosporine regimens were associated with a lower incidence of tumors than was standard therapy.²⁶ The risk among patients with heart transplants, who generally receive higher levels of immunosuppressive therapy than do other transplant recipients, is three times as high as the risk among renal-transplant recipients.⁶ Patients with liver transplants, who often receive lower levels of immunosuppressive therapy than do other transplant recipients, have a lower risk of skin carcinoma.²⁷ Patients receiving the same immunosuppressive regimen may have different levels of immunosuppression because of individual genetic variations or other factors. For example, variations in thiopurine methyltransferase activity may result in variable responsiveness to azathioprine.²⁸ The risk of skin cancer in transplant recipients who are taking the newer immunosuppressive drugs is unknown, since skin cancers occur several years after transplantation. Available evidence suggests that at least one of these drugs, sirolimus, may confer a lower risk than standard therapy.^{29,30}



Figure 1. Squamous-Cell Carcinomas in Transplant Recipients.

Panel A shows squamous-cell carcinoma of the helix associated with pre-malignant keratoses and warts in a male recipient of a heart graft. Panel B shows multiple pre-malignant keratoses and squamous-cell carcinomas of the dorsum of the hand in a male recipient of a renal graft. Panel C shows aggressive (metastatic) squamous-cell carcinoma of the toe in a 32-year-old woman who underwent renal transplantation at the age of 16 years.

Human papillomaviruses (HPV) also may be co-carcinogenic. Squamous-cell carcinomas are frequently associated with warts and may have histologic features of HPV infection.³¹ HPV DNA is detected in 65 to 90 percent of squamous-cell carcinomas from transplant recipients,³² and the percentage of HPV-containing tumors appears to increase with the number of squamoproliferative lesions.³³ In one study, the rate of HPV detection in clinically normal, sun-exposed skin was higher among transplant recipients with skin cancer than among those without skin cancer.³⁴ Tumors from transplant recipients contain various HPV strains, including not only those related to epidermodysplasia verruciformis, but also common benign cutaneous strains (HPV types 1 and 2) and mucosal strains, both oncogenic (HPV types 16 and 18) and nononcogenic (HPV types 6 and 11).³¹⁻³⁴ Frequently, several HPV strains are detected within a single tumor. Persistent infection with both oncogenic and nononcogenic HPV strains is carcinogenic.³⁵ However, the role of HPV in the development of skin cancer is still not definitively settled, because HPV is frequently present in hair follicles in normal skin from transplant recipients³⁶; furthermore, long-lasting warts in transplant recipients do not necessarily progress to skin cancer.

Additional factors reported to be associated with an increased risk of skin cancer include the duration of pretransplantation dialysis (in renal-transplant

recipients²) and, possibly, smoking,^{16,37} as in the general population.³⁸ Despite contradictory data,³⁹ several studies suggest an association of the p53 polymorphism with susceptibility to squamous-cell carcinomas.⁴⁰⁻⁴² The role of other factors, including genetic variation in enzymes involved in free-radical metabolism,^{37,43} HLA class I or II homozygosity, HLA mismatching,⁴⁴ and loss of heterozygosity of the Rb locus,⁴⁵ remains controversial.

MANAGEMENT

The management of skin carcinomas in transplant recipients depends on the type of lesion and its extent (Table 2). Superficial tumors can be managed with cryotherapy or electrocautery and curettage. For thicker lesions, surgical excision with histologic examination is the treatment of choice, allowing accurate diagnosis, verification of excised margins, and assessment of the aggressiveness of the tumor. Guidelines for the margins of excision of squamous-cell carcinomas have not been established for transplant recipients. For that reason, Mohs' micrographic surgery is recommended for high-risk tumors (those with a cephalic location, a diameter of more than 2 cm, or rapid growth) and for locally recurring tumors. Reconstruction with flaps and grafts may be required for large tumors, especially on the face and the hands. Metastasis to a single regional lymph node, in the absence of extracapsular spread, can be cured by lymphadenectomy alone.

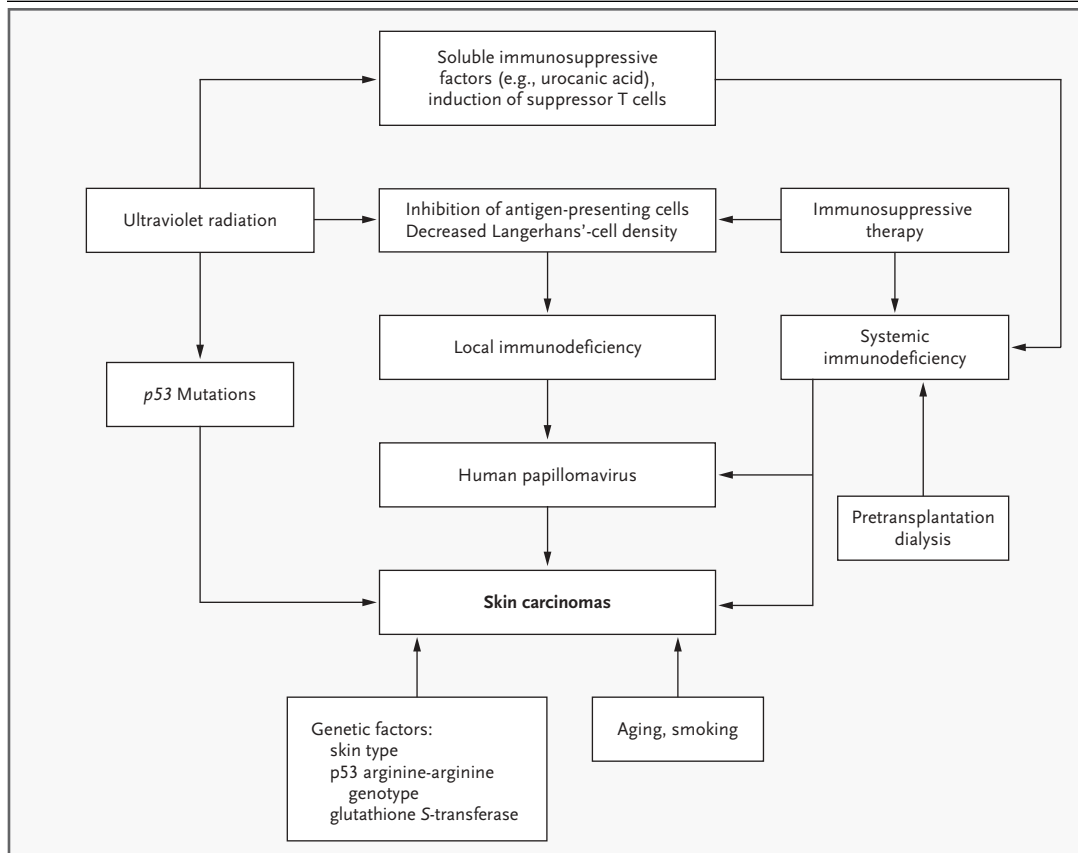


Figure 2. Suggested Mechanisms of Skin Carcinogenesis in Transplant Recipients.

Ultraviolet radiation generates mutations in the *p53* gene, secretion of immunosuppressive factors, and inhibition of antigen-presenting cells and Langerhans' cells. Immunosuppressive treatments also inhibit antigen-presenting cells (including Langerhans' cells). Local and systemic immunodeficiency (enhanced by pretransplantation dialysis) favor the proliferation of human papillomavirus, which acts as a cocarcinogen. Genetic factors (such as fair skin, polymorphism in *p53*, and glutathione *S*-transferase), aging, and smoking may have a direct effect on the generation of cutaneous carcinomas.

Adjuvant radiotherapy appears to be beneficial if more than one node is positive or if extracapsular spread has occurred. Combination chemotherapy with isotretinoin and interferon alfa, recommended for aggressive squamous-cell carcinomas,⁴⁶ may be useful for kidney-transplant recipients¹⁴ and liver-transplant recipients, despite the risk of acute rejection associated with interferon alfa.⁴⁷ Metastatic tumors can be treated with chemotherapy (bleomycin, fluorouracil, and cisplatin), but responses to treatment are often poor.¹⁸

To reduce the risk of new tumors, additional therapeutic measures may be required after a squamous-cell carcinoma has been excised. Tapering immunosuppressive treatment usually decreases the rate of cutaneous carcinogenesis and is there-

fore recommended for patients with multiple or aggressive lesions.^{14,48,49} The risk of graft rejection should be considered, but it appears to be lower than originally feared.^{14,17} Systemic retinoids (etretinate and acitretin) appear to reduce actinic keratoses and prevent the development of new dysplastic lesions in transplant recipients.⁵⁰⁻⁵² However, retinoids must often be discontinued because of side effects such as mucocutaneous xerosis, pruritus, arthralgias, and hyperlipidemia. Although retinoids do not interfere with the metabolism of cyclosporine, their role in inducing rejection episodes has not been ruled out.⁵³ Alone or in combination with low-dose systemic retinoids, topical retinoids (tretinoin and adapalene) are reported to be effective for the treatment of premalignant lesions.^{54,55} Top-

Table 2. Management of Skin Carcinomas in Transplant Recipients.

Tumor Type	First-Line Treatment	Adjuvant Local Treatment	Systemic Treatment	Reduction of Immunosuppressive Treatment
Actinic keratosis, superficial basal-cell carcinoma, Bowen's disease	Cryotherapy, electrocautery, curettage, laser treatment, fluorouracil	Topical retinoids (in the case of multiple lesions)	—	—
Basal-cell and squamous-cell carcinoma, keratoacanthoma	Excision	—	—	—
Multiple squamous-cell carcinomas	Excision	—	Oral retinoids	Recommended
High-risk squamous-cell carcinoma	Excision or Mohs' surgery	—	—	—
Local recurrence of squamous-cell carcinoma	Excision or Mohs' surgery	—	—	Recommended
Metastatic squamous-cell carcinoma	Excision, lymphadenectomy	Radiotherapy	Chemotherapy and, possibly, oral retinoids or interferon alfa	Required

ical application of one of the new immune-response modifiers, such as imiquimod or resiquimod, over a period of several weeks appears to be a promising treatment for superficial basal-cell carcinomas and actinic keratoses,^{53,56} but the efficacy and safety of these agents in transplant recipients have not been assessed in controlled trials.

CANCERS OF THE
ANOGENITAL REGION

Cancers of the anogenital region reportedly represent 2.8 percent of cancers in transplant recipients, and the incidence of such cancers is increased by a factor of 30 to 100 as compared with the incidence in the general population.⁵⁷⁻⁵⁹ Anogenital cancers are the fourth most frequent malignant condition in patients who underwent transplantation in childhood.¹⁹ The mean interval between transplantation and diagnosis is seven years, and the ratio of affected females to affected males is 2:1. The ratio is even higher in patients who received allografts as children, in whom lesions often develop during adulthood (mean interval after transplantation, 142 months for carcinomas of the vulva and perineum).¹⁹ Additional risk factors include multiple sexual partners, HPV infection, a history of herpes genitalis, heavy smoking, the presence of skin cancers elsewhere, and a high level of immunosuppression.^{33,57,60}

The lesions tend to be multiple, extensive, or both, especially in women, one third of whom have concomitant cervical cancer. Clinically, the lesions often appear as pigmented papular lesions, with histologic features of Bowen's disease (bowenoid papulosis) (Fig. 3), but may resemble genital warts. For that reason, persistent, refractory wart-like lesions should be examined histologically. In the largest reported series,⁵⁷ lesions ranged from in situ carcinoma (in one third of patients) to invasive tumors with regional lymph-node metastases (in 11 percent).⁵⁷

In situ anogenital cancers can be treated with laser therapy, electrocautery, and topical fluorouracil. Treatment with topical imiquimod, which is marketed for the treatment of anogenital warts, may be helpful but needs further assessment. Invasive tumors require wide surgical excision (e.g., radical vulvectomy), inguinal lymphadenectomy (for tumors that are more than 1 mm thick), and adjuvant radiotherapy, chemotherapy, or both.⁶¹ Tapering the immunosuppressive regimen is beneficial and by itself may lead to the resolution of in situ carcinoma.⁶⁰

KAPOSI'S SARCOMA

The incidence of Kaposi's sarcoma is much higher in transplant recipients than in nonimmunosuppressed populations (by a factor of 84 to 500).^{6,62,63}



Figure 3. Bowenoid Papulosis Manifested as Coalescent Brown Papules of the Genitalia in a Lung-Transplant Recipient.

Most cases occur in transplant recipients of Mediterranean, Jewish, Arabic, Caribbean, or African descent; the reported incidence ranges from 0.5 percent in most Western countries (including the United States⁶⁴) to 5.3 percent in Saudi Arabia.⁶⁵

Kaposi's sarcoma usually appears early (a mean interval of 13 months after transplantation)⁶³ but has been documented as late as 18 years afterward. The ratio of male patients to female patients is 3.3 to 1.0; the mean age at the time of diagnosis is 43 years, which is younger than that among patients with classic Kaposi's sarcoma. Cases have been reported even in children with transplants.⁶⁶

Ninety percent of transplant recipients with Kaposi's sarcoma have cutaneous or mucosal lesions or both types. Visceral involvement occurs in 25 to 30 percent of patients with kidney transplants and in 50 percent of those with heart or liver transplants.⁶⁷ Purely visceral disease occurs in 10 percent of patients.⁶⁸ A grading system (grades I through IV) has been proposed to reflect the extent of the disease.⁶⁹ Post-transplantation Kaposi's sarcoma is usually similar to the classic form, manifested as

angiomatous lesions predominating on the legs and causing lymphedema (Fig. 4). The oropharyngeal and conjunctival mucosa may be affected.⁶⁸ Visceral disease predominantly affects the lymph nodes, gastrointestinal tract, and lungs.⁶⁸

CAUSE AND PATHOGENESIS

A viral cause of Kaposi's sarcoma has long been suspected, and it was confirmed in 1994 by the discovery of a new herpesvirus, Kaposi's sarcoma-associated herpesvirus, or human herpesvirus 8 (HHV-8). HHV-8 is an oncogenic gamma-herpesvirus encoding for cytokines and factors involved in cell proliferation, apoptosis, and immune responses and exerting a transformative effect on human endothelial cells.⁷⁰ Although HHV-8 is almost invariably present in affected tissues and occasionally also in normal skin from patients with Kaposi's sarcoma, it disappears from scar tissue in old lesions that have regressed.⁷¹ HHV-8 is also detected in peripheral-blood mononuclear cells, where the viral load is correlated with the stage and progression of disease.⁷²

The preponderance of cases of Kaposi's sarcoma in certain ethnic groups appears to be linked to the geographic distribution of HHV-8 infection, since its prevalence parallels HHV-8 seroprevalence (less than 5 percent in North America, northern Europe, and Asia; 5 to 20 percent in the Mediterranean, the Middle East, and the Caribbean; and more than 50 percent in central and southern Africa).^{64,73-75} Most cases of post-transplantation Kaposi's sarcoma apparently develop as a result of viral reactivation, since more than 80 percent of transplant recipients with Kaposi's sarcoma are seropositive for HHV-8 before undergoing transplantation.^{73,74} Among patients who are seropositive for HHV-8 before undergoing kidney transplantation, the risk of post-transplantation Kaposi's sarcoma is 23 to 28 percent,^{76,77} as compared with a risk of 0.7 percent in patients who are seronegative before receiving a kidney transplant.⁷³ Thus, pretransplantation antibody screening appears to be useful for identifying high-risk patients. However, seroepidemiologic data suggest that HHV-8 can also be transmitted from the donor⁷⁸; therefore, donor testing may be warranted as a prophylactic measure against HHV-8 transmission, particularly in areas with high HHV-8 seroprevalence.⁷⁴

The course of Kaposi's sarcoma depends on the level of immunosuppression; the lesions regress on discontinuation of immunosuppressive therapy.



Figure 4. Kaposi's Sarcoma Lesions on the Leg of a Man with a Liver Transplant.

However, the condition usually, but not invariably,⁷⁹ recurs after retransplantation and reintroduction of immunosuppressive treatment. The estimated survival rate at five years is 69 percent,⁶³ but it varies according to the extent of the disease. The survival rate at one year is 90 percent for cutaneous disease, but 70 percent for visceral forms. Patients with Kaposi's sarcoma who have heart or liver transplants appear to have a shorter survival than those with kidney allografts.^{67,80} Patients in the United States appear to have a more favorable prognosis than those in other parts of the world, a finding that is probably related to the lower rate of visceral involvement in the United States.⁶³

MANAGEMENT

The first step in the treatment of post-transplantation Kaposi's sarcoma is to reduce the level of immunosuppression, which is likely to result in partial or complete regression of the lesions. In cases of progressive disease, discontinuation of immunosuppressive treatment in consultation with transplantation physicians might be attempted, espe-

cially in patients with kidney or liver transplants. Additional treatment, which is required in the case of persistent functional disability or life-threatening disease,⁸¹ may include chemotherapy with vincristine or vinblastine, bleomycin, and doxorubicin (singly or in various combinations)⁸²; liposomal daunorubicin; paclitaxel; etoposide; dactinomycin; and cisplatin. Radiotherapy and interferon alfa may be effective, but interferon alfa should be used with caution, because of the risk of graft rejection.⁴⁷ Isolated lesions can be excised surgically or treated with cryotherapy. The clinical usefulness of antiviral drugs (foscarnet, ganciclovir, cidofovir, and adefovir) that have in vitro activity against HHV-8 has not yet been adequately documented.

MELANOMA

Although transplant recipients appear to be at lower risk for melanoma than for other skin cancers, the risk has been reported to be increased by a factor of 1.6 to 3.4 in Europe^{6,59,83} and by a factor of 2 to 4 in Australia, as compared with the risk in the general population.^{5,58} Melanomas occur mainly in patients with fair complexion, light hair and eyes, and a tendency to freckle. Nevi in large numbers may be a risk factor for melanoma in renal-transplant recipients, especially children.^{19,20} The mean interval between transplantation and the diagnosis of melanoma is five years, and there may be multiple lesions.^{5,84} Thirty-five percent of transplant recipients with melanoma have other cancers.⁸⁴ Melanoma accounts for 6.2 percent of post-transplantation skin cancers in adults and for 15 percent in children.⁸⁴ The prognosis depends on the thickness of the tumor, but whether, for tumors of similar thickness, the course is more severe in transplant recipients than in other patients remains uncertain.

Along with a reduction in the level of immunosuppression, treatment includes wide surgical excision and possible excisional biopsy of a sentinel lymph node, depending on the histologic features of the primary tumor. In the rare patient with pre-transplantation melanoma, the risk of recurrence after transplantation is high (20 percent), even if the primary lesion occurred as long as 10 years before transplantation.⁸⁴ For this reason, a prolonged waiting period before performing transplantation is advisable for a patient with antecedent melanoma (except for in situ melanoma). The length of the waiting period should be weighed against other risks, especially for patients awaiting a heart, lung,

or liver transplant. Finally, melanoma may be transmitted inadvertently from donors with cerebral metastatic melanoma misdiagnosed as a brain tumor or cerebral hemorrhage at the time of death. In such cases, complete remission may follow removal of the transplant and discontinuation of immunosuppressive treatment.⁸⁴

NEUROENDOCRINE SKIN
CARCINOMA
(MERKEL-CELL CARCINOMA)

Fifty-five cases of neuroendocrine skin carcinoma have been reported in transplant recipients, who appear to be at higher risk for this type of skin cancer than the general population.^{85,86} Other cutaneous and extracutaneous tumors were found in half these patients.

Neuroendocrine skin carcinoma is manifested as an asymptomatic, nonspecific nodular growth. It occurs predominantly in male transplant recipients, and the mean age at the time of diagnosis (53 years) is younger than that in nonimmunosuppressed patients. The lesion develops an average of 7.5 years after transplantation and is usually located on the head or neck and the arms. This fact, along with the frequent association with other skin carcinomas, suggests that exposure to sun is a precipitating factor.

Treatment consists of surgical excision with 2-cm margins or Mohs' surgery. Sentinel lymph-node biopsy is required, because two thirds of patients have lymph-node metastases.⁸⁷ Lymphadenectomy, possibly with radiotherapy and chemotherapy, is usually recommended. Distant metastases may regress temporarily after the cessation of treatment with cyclosporine.⁸⁸ However, the overall prognosis is poor, with a mortality rate of 56 percent at two years (as compared with 25 to 35 percent among nonimmunosuppressed patients).

LYMPHOMAS

Lymphomas are among the most common complications of transplantation, affecting up to 5 percent of all transplant recipients. Many cases are related to Epstein-Barr virus (EBV).⁸⁹ It has recently been suggested that HHV-8 may be responsible for some lymphomas that are unrelated to EBV.⁹⁰ Purely cutaneous lymphomas are rare, with fewer than 30 cases reported.⁸⁵ In contrast to extracutaneous lymphomas,

cutaneous lymphomas usually occur in men and at a later interval after transplantation (five years).

Seventy percent of cutaneous lymphomas are B-cell lymphomas in origin, presenting as single or multiple papules or nodules on the face, trunk, or limbs, which are occasionally ulcerated. Histologically, such lesions consist of a dermal, nonepidermotropic infiltrate of lymphocytes expressing B-cell antigens and, occasionally, CD30. Molecular studies most often reveal a clonal rearrangement of immunoglobulin heavy chains and the presence of EBV.⁹¹ Remission may occur after immunosuppressive treatment has been tapered.⁹¹ The prognosis generally seems to be better in the absence of extracutaneous involvement, although there are exceptions.⁹² Treatment includes surgical excision, radiotherapy, chemotherapy, and the administration of interferon alfa, acyclovir, or both, along with a decrease in the level of immunosuppression.⁹¹

The other 30 percent of cutaneous lymphomas are T-cell lymphomas in origin, manifested clinically as mycosis fungoides, erythroderma, or hemorrhagic lesions, usually with generalized lymphadenopathy.⁹³ Histologically, these lesions consist of an epidermotropic dermal infiltrate of CD3+ cells. Molecular studies reveal a clonal rearrangement of the T-cell receptor but no EBV genome. Cutaneous T-cell lymphomas can be associated with EBV-positive nodal lymphoma.⁹³ Treatment is unsatisfactory, although promising possibilities are emerging (rituximab, local or systemic bexarotene, and denileukin diftitox). The prognosis is worse for cutaneous T-cell lymphomas than for B-cell lymphomas.

SARCOMAS

Cutaneous sarcomas other than Kaposi's sarcoma have been reported in transplant recipients.⁹⁴ However, the small number of reported cases prevents conclusions about their incidence and whether it is higher in such patients than in the general population. These tumors include angiosarcomas, fibroxanthomas, leiomyosarcomas, and dermatofibrosarcoma protuberans.

Angiosarcomas are manifested as tender violaceous masses occurring most often in the region of previously placed hemodialysis fistulas.⁹⁵ Other sites have included the scalp and the transplantation wound. Bullous lymphangiosarcoma may also occur. Despite surgical treatment, the prognosis for

patients with such lesions appears to be poor, with death occurring an average of 13 months after diagnosis.⁸⁵

The appearance of malignant fibrous histiocytoma and its superficial variant, atypical fibroxanthoma,⁹⁶ mimics basal- or squamous-cell carcinoma. It is often associated with premalignant keratoses or overt cutaneous carcinomas. Surgical excision with adequate margins is necessary to prevent recurrence.⁹⁷ Isolated cases of leiomyosarcomas and dermatofibrosarcoma protuberans have been reported in transplant recipients.⁸⁵

CONCLUSIONS

Skin cancers, which are the most common tumors after solid-organ transplantation, cause serious morbidity and may have a life-threatening course.

Along with specific treatment, such tumors may require the tapering of immunosuppressive treatment. Squamous-cell carcinomas account for the majority of skin cancers in transplant recipients and are mainly related to sun exposure. Prevention of these tumors starts with adequate education of patients about the importance of strict protection from the sun.^{98,99} All patients must avoid direct exposure to the sun, use appropriate clothing for outdoor activities (i.e., a large-brimmed hat, long sleeves, and long pants), and apply sunscreens with a high sun-protection factor. An increasing number of transplantation units provide patients with detailed written recommendations for protecting themselves from the sun. Prevention also includes regular dermatologic monitoring for early detection and ablation of premalignant lesions.^{49,100} Such measures may prevent many skin cancers.

REFERENCES

1. Webb MC, Compton F, Andrews PA, Koffman CG. Skin tumours posttransplantation: a retrospective analysis of 28 years' experience at a single centre. *Transplant Proc* 1997;29:828-30.
2. Hiesse C, Rieu P, Kriaa F, et al. Malignancy after renal transplantation: analysis of incidence and risk factors in 1700 patients followed during a 25-year period. *Transplant Proc* 1997;29:831-3.
3. Winkelhorst JT, Brokelman WJ, Tiggeler RG, Wobbes T. Incidence and clinical course of de-novo malignancies in renal allograft recipients. *Eur J Surg Oncol* 2001;27:409-13.
4. Sanchez EQ, Marubashi S, Jung G, et al. De novo tumors after liver transplantation: a single-institution experience. *Liver Transplant* 2002;8:285-91.
5. Bouwes-Bavinck JN, Hardie DR, Green A, et al. The risk of skin cancer in renal transplant recipients in Queensland, Australia: a follow-up study. *Transplantation* 1996;61:715-21.
6. Jensen P, Hansen S, Moller B, et al. Skin cancer in kidney and heart transplant recipients and different long-term immunosuppressive therapy regimens. *J Am Acad Dermatol* 1999;40:177-86.
7. Hartevelt MM, Bavinck JN, Kootte AMM, Vermeer BJ, Vandenbroucke JP. Incidence of skin cancer after renal transplantation in the Netherlands. *Transplantation* 1990;49:506-9.
8. Ramsay HM, Fryer AA, Hawley CM, Smith AG, Harden PN. Non-melanoma skin cancer risk in the Queensland renal transplant population. *Br J Dermatol* 2002;147:950-6.
9. Lindelöf B, Sigurgeirsson B, Gäbel H, Stern RS. Incidence of skin cancer in 5356 patients following organ transplantation. *Br J Dermatol* 2000;143:513-9.
10. Euvrard S, Kanitakis J, Pouteil-Noble C, et al. Comparative epidemiologic study of premalignant and malignant epithelial cutaneous lesions developing after kidney and heart transplantation. *J Am Acad Dermatol* 1995;33:222-9.
11. Ishikawa N, Tanabe K, Tokumoto T, et al. Clinical study of malignancies after renal transplantation and impact of routine screening for early detection: a single-center experience. *Transplant Proc* 2000;32:1907-10.
12. Liddington M, Richardson AJ, Higgins RM, et al. Skin cancer in renal transplant recipients. *Br J Surg* 1989;76:1002-5.
13. Cooper SM, Wojnarowska F. The accuracy of clinical diagnosis of suspected premalignant and malignant skin lesions in renal transplant recipients. *Clin Exp Dermatol* 2002;27:436-8.
14. Euvrard S, Kanitakis J, Pouteil-Noble C, et al. Aggressive squamous cell carcinomas in organ transplant recipients. *Transplant Proc* 1995;27:1767-8.
15. Adamson R, Obispo E, Dychter S, et al. High incidence and clinical course of aggressive skin cancer in heart transplant patients: a single-center study. *Transplant Proc* 1998;30:1124-6.
16. Pollard JD, Hanasono MM, Mikulec AA, Le QT, Terris DJ. Head and neck cancer in cardiothoracic transplant recipients. *Laryngoscope* 2000;110:1257-61.
17. Veness MJ, Quinn DI, Ong CS, et al. Aggressive cutaneous malignancies following cardiothoracic transplantation: the Australian experience. *Cancer* 1999;85:1758-64.
18. Martinez JC, Otley CC, Stasko T, et al. Defining the clinical course of metastatic skin cancer in organ transplant recipients: a multicenter collaborative study. *Arch Dermatol* 2003;139:301-6.
19. Penn I. De novo malignancies in pediatric organ transplant recipients. *Pediatr Transplant* 1998;2:56-63.
20. Euvrard S, Kanitakis J, Cochat P, Cambazard F, Claudy A. Skin diseases in children with organ transplants. *J Am Acad Dermatol* 2001;44:932-9.
21. Bavinck JN, De Boer A, Vermeer BJ, et al. Sunlight, keratotic skin lesions and skin cancer in renal transplant recipients. *Br J Dermatol* 1993;129:242-9.
22. Espana A, Martinez-Gonzalez MA, Garcia-Granero M, Sanchez-Carpintero I, Rabago G, Herreros J. A prospective study of incident nonmelanoma skin cancer in heart transplant recipients. *J Invest Dermatol* 2000;115:1158-60.
23. McGregor JM, Berkhout RJM, Rozycka M, et al. p53 Mutations implicate sunlight in post-transplant skin cancer irrespective of human papillomavirus status. *Oncogene* 1997;15:1737-40.
24. Ducloux D, Carron PL, Rebibou JM, et al. CD4 lymphocytopenia as a risk factor for skin cancers in renal transplant recipients. *Transplantation* 1998;65:1270-2.
25. Caforio AL, Fortina AB, Piaserico S, et al. Skin cancer in heart transplant recipients: risk factor analysis and relevance of immunosuppressive therapy. *Circulation* 2000;102:Suppl III:III-222-III-227.
26. Dantal J, Hourmant M, Cantarovich D, et al. Effect of long-term immunosuppression in kidney-graft recipients on cancer incidence: randomised comparison of two cyclosporin regimens. *Lancet* 1998;351:623-8.
27. Frezza EE, Fung JJ, van Thiel DH. Non-lymphoid cancer after liver transplantation. *Hepatogastroenterology* 1997;44:1172-81.
28. Chocair PR, Duley JA, Simmonds HA, Cameron JS. The importance of thiopurine methyltransferase activity for the use of azathioprine in transplant recipients. *Transplantation* 1992;53:1051-6.
29. Guba M, von Breitenbuch P, Steinbauer M, et al. Rapamycin inhibits primary and

- metastatic tumor growth by antiangiogenesis: involvement of vascular endothelial growth factor. *Nat Med* 2002;8:128-35.
30. Luan FL, Hojo M, Maluccio M, Yamaji K, Suthanthiran M. Rapamycin blocks tumor progression: unlinking immunosuppression from antitumor efficacy. *Transplantation* 2002;73:1565-72.
31. Euvrard S, Chardonnet Y, Pouteil-Noble C, et al. Association of skin malignancies with various and multiple carcinogenic and non carcinogenic human papillomaviruses in renal transplant recipients. *Cancer* 1993;72:2198-206.
32. Harwood CA, Suretheran T, McGregor JM, et al. Human papillomavirus infection and non-melanoma skin cancer in immunosuppressed and immunocompetent individuals. *J Med Virol* 2000;61:289-97.
33. Arends MJ, Benton EC, McLaren KM, Stark LA, Hunter JA, Bird CC. Renal allograft recipients with high susceptibility to cutaneous malignancy have an increased prevalence of human papillomavirus DNA in skin tumours and a greater risk of anogenital malignancy. *Br J Cancer* 1997;75:722-8.
34. de Jong-Tieben LM, Berkhout R, ter Schegget J, et al. The prevalence of human papillomavirus DNA in benign keratotic skin lesions of renal transplant recipients with and without a history of skin cancer is equally high: a clinical study to assess risk factors for keratotic skin lesions and skin cancer. *Transplantation* 2000;69:44-9.
35. Berkhout R, Bouwes Bavinck J, ter Schegget J. Persistence of human papillomavirus DNA in benign and (pre)malignant skin lesions from renal transplant recipients. *J Clin Microbiol* 2000;38:2087-96.
36. Boxman ILA, Berkhout RJM, Mulder LHC, et al. Detection of human papillomavirus DNA in plucked hairs from renal transplant recipients and healthy volunteers. *J Invest Dermatol* 1997;108:712-5.
37. Ramsay HM, Harden RN, Reece S, et al. Polymorphism in glutathione S-transferases are associated with altered risk of nonmelanoma skin cancer in renal transplant recipients: a preliminary analysis. *J Invest Dermatol* 2001;117:251-5.
38. De Hertog SA, Wensveen CA, Bastiaens MT, et al. Relation between smoking and skin cancer. *J Clin Oncol* 2001;19:231-8.
39. Marshall SE, Bordea C, Wojnarowska F, Morris PJ, Welsh KI. p53 Codon 72 polymorphism and susceptibility to skin cancer after renal transplantation. *Transplantation* 2000;69:994-6.
40. Storey A, Thomas M, Kalita A, et al. Role of a p53 polymorphism in the development of human papillomavirus-associated cancer. *Nature* 1998;393:229-34.
41. Cairey-Remonnay S, Humbey O, Mougin C, et al. TP53 polymorphism of exon 4 at codon 72 in cutaneous squamous cell carcinoma and benign epithelial lesions of renal transplant recipients and immunocompetent individuals: lack of correlation with human papillomavirus status. *J Invest Dermatol* 2002;118:1026-31.
42. McGregor JM, Harwood CA, Brooks L, et al. Relationship between p53 codon 72 polymorphism and susceptibility to sunburn and skin cancer. *J Invest Dermatol* 2002;119:84-90.
43. Marshall SE, Bordea C, Haldar N, et al. Glutathione S-transferase polymorphisms and skin cancer after renal transplantation. *Kidney Int* 2000;58:2186-93.
44. Bouwes Bavinck JN, Claas FH, Hardie DR, Green A, Vermeer BJ, Hardie IR. Relation between HLA antigens and skin cancer in renal transplant recipients in Queensland, Australia. *J Invest Dermatol* 1997;108:708-11.
45. O'Connor DP, Kay EW, Leader M, Murphy GM, Atkins GJ, Mabruk MJ. A high degree of chromosomal instability at 13q14 in cutaneous squamous cell carcinomas: indication for a role of a tumour suppressor gene other than Rb. *Mol Pathol* 2001;54:165-9.
46. Lippman SM, Parkinson DR, Itri LM, et al. 13-cis-Retinoic acid and interferon alpha-2a: effective combination therapy for advanced squamous cell carcinoma of the skin. *J Natl Cancer Inst* 1992;84:235-41.
47. Magnone M, Holley JL, Shapiro R, et al. Interferon- α -induced acute renal allograft rejection. *Transplantation* 1995;59:1068-70.
48. Otley CC, Coldiron BM, Stasko T, Goldman GD. Decreased skin cancer after cessation of therapy with transplant-associated immunosuppressants. *Arch Dermatol* 2001;137:459-63.
49. Berg D, Otley CC. Skin cancer in organ transplant recipients: epidemiology, pathogenesis, and management. *J Am Acad Dermatol* 2002;47:1-17.
50. Euvrard S, Kanitakis J, Thivolet J, et al. Retinoids for the management of dermatological complications of organ transplantation. *Biodrugs* 1997;3:176-84.
51. Bavinck JN, Tieben LM, Van der Woude FJ, et al. Prevention of skin cancer and reduction of keratotic skin lesions during acitretin therapy in renal transplant recipients: a double-blind, placebo-controlled study. *J Clin Oncol* 1995;13:1933-8.
52. McKenna DB, Murphy GM. Skin cancer chemoprophylaxis in renal transplant recipients: 5 years of experience using low-dose acitretin. *Br J Dermatol* 1999;140:656-60.
53. Rook AH, Shapiro M. Cutaneous squamous-cell carcinoma. *N Engl J Med* 2001;345:296.
54. Rook AH, Jaworsky C, Nguyen T, et al. Beneficial effect of low-dose systemic retinoid in combination with topical tretinoin for the treatment and prophylaxis of premalignant and malignant skin lesions in renal transplant recipients. *Transplantation* 1995;59:714-9.
55. Euvrard S. Topical retinoids for the management of dysplastic epithelial lesions. In: Euvrard S, Kanitakis J, Claudy A, eds. *Skin diseases after organ transplantation*. Paris: John Libbey Eurotext, 1998:175-82.
56. Stockfleth E, Ulrich C, Meyer T, Christophers E. Epithelial malignancies in organ transplant patients: clinical presentation and new methods of treatment. *Recent Results Cancer Res* 2002;160:251-8.
57. Penn I. Cancers of the anogenital region in renal transplant recipients: analysis of 65 cases. *Cancer* 1986;58:611-6.
58. Sheil AGR, Flavel S, Disney APS, Mathew TH, Hall BM. Cancer incidence in renal transplant patients treated with azathioprine or cyclosporine. *Transplant Proc* 1987;19:2214-6.
59. Birkeland SA, Storm HH, Lamm LU, et al. Cancer risk after renal transplantation in nordic countries. *Int J Cancer* 1995;60:183-9.
60. Euvrard S, Kanitakis J, Chardonnet Y, et al. External anogenital lesions in organ transplant recipients: a clinicopathologic and virologic assessment. *Arch Dermatol* 1997;133:175-8.
61. Sillman FH, Sentovich S, Shaffer D. Anogenital neoplasia in renal transplant patients. *Ann Transplant* 1997;2:59-66.
62. Harwood AR, Osoba D, Hofstader SL, et al. Kaposi's sarcoma in recipients of renal transplants. *Am J Med* 1979;67:759-65.
63. Woodle E, Hanaway M, Buell J, et al. Kaposi's sarcoma: an analysis of the US and international experiences from the Israel Penn International Transplant Tumor Registry. *Transplant Proc* 2001;33:3660-1.
64. Jenkins FJ, Hoffman LJ, Liegey-Dougall A. Reactivation of and primary infection with human herpesvirus 8 among solid-organ transplant recipients. *J Infect Dis* 2002;185:1238-43.
65. Qunibi W, Akhtar M, Sheth K, et al. Kaposi's sarcoma: the most common tumor after renal transplantation in Saudi Arabia. *Am J Med* 1988;84:225-32.
66. Ozen S, Saatci U, Karaduman A, et al. Kaposi's sarcoma in a paediatric renal transplant recipient. *Nephrol Dial Transplant* 1996;11:1162-3.
67. Farge D. Kaposi's sarcoma in organ transplant recipients. *Eur J Med* 1993;2:339-43.
68. Penn I. Kaposi's sarcoma in transplant recipients. *Transplantation* 1997;64:669-73.
69. Al-Khader A, Suleiman M, Al-Hassani M, Haleem A. Posttransplant Kaposi sarcoma: staging as a guide to therapy and prognosis. *Nephron* 1988;48:165.
70. Boshoff C, Weiss RA. Epidemiology and pathogenesis of Kaposi's sarcoma-associated herpesvirus. *Philos Trans R Soc Lond Biol Sci* 2001;356:517-34.
71. Noël JC, De Thier F, Heenen M, Fayt I, Abramowicz D, Doutreloup JM. HHV-8 is associated with recurrent Kaposi's sarcoma in a renal transplant recipient. *Transpl Int* 1997;10:81-2.
72. Pellet C, Chevret S, Francès C, et al. Prognostic value of quantitative Kaposi sarcoma-associated herpesvirus load in post-transplantation Kaposi sarcoma. *J Infect Dis* 2002;186:110-3.

73. Cattani P, Capuano M, Graffeo R, et al. Kaposi's sarcoma associated with previous human herpesvirus 8 infection in kidney transplant recipients. *J Clin Microbiol* 2001; 39:506-8.
74. Allen U. Human herpesvirus type 8 infections among solid organ transplant recipients. *Pediatr Transplant* 2002;6:187-92.
75. Moore PS. The emergence of Kaposi's sarcoma-associated herpesvirus (human herpesvirus 8). *N Engl J Med* 2000;343:1411-3.
76. Francès C, Mouquet C, Marcellin AG, et al. Outcome of kidney transplant recipients with previous human herpesvirus-8 infection. *Transplantation* 2000;69:1776-9.
77. Emond JP, Marcellin AG, Dorent R, et al. Kaposi's sarcoma associated with previous human herpesvirus 8 infection in heart transplant recipients. *J Clin Microbiol* 2002; 40:2217-9.
78. Regamey N, Tamm M, Wernli M, et al. Transmission of human herpesvirus 8 infection from renal-transplant donors to recipients. *N Engl J Med* 1998;339:1358-63.
79. Euvrard S, Kanitakis J, Brosshard C, et al. No recurrence of posttransplantation Kaposi's sarcoma three years after renal retransplantation. *Transplantation* 2002;73: 297-9.
80. Aseni P, Vertemati M, Minola E, et al. Kaposi's sarcoma in liver transplant recipients: morphological and clinical description. *Liver Transpl* 2001;7:816-23.
81. Barete S, Calvez V, Mouquet C, et al. Clinical features and contribution of virological findings to the management of Kaposi sarcoma in organ-allograft recipients. *Arch Dermatol* 2000;136:1452-8.
82. Shepherd FA, Maher E, Cardella C, et al. Treatment of Kaposi's sarcoma after solid organ transplantation. *J Clin Oncol* 1997; 15:2371-7.
83. Lévêque L, Dalac S, Dompormartin A, et al. Mélanome chez le transplanté. *Ann Dermatol Venerol* 2000;127:160-5.
84. Penn I. Malignant melanoma in organ allograft recipients. *Transplantation* 1996; 61:274-8.
85. Euvrard S, Kanitakis J, Claudy A. Neoplastic skin diseases in organ transplant recipients. *Am J Cancer* 2002;1:109-20.
86. Penn I, First MR. Merkel's skin carcinoma in organ recipients: report of 41 cases. *Transplantation* 1999;68:1717-21.
87. Mehrany K, Otley CC, Weenig RH, Phillips PK, Roenigk RK, Nguyen TH. A meta-analysis of the prognostic significance of sentinel lymph node status in Merkel cell carcinoma. *Dermatol Surg* 2002;28:113-7.
88. Friedlaender MM, Rubinger D, Rosenbaum E, Amir G, Siguencia E. Temporary regression of Merkel cell carcinoma metastases after cessation of cyclosporine. *Transplantation* 2002;73:1849-50.
89. De Carlis L, Slim A, De Gasperi A, et al. Posttransplant lymphoproliferative disorders: report from a single center. *Transplant Proc* 2001;33:2815-6.
90. Kapelushnik J, Ariad S, Benharroch D, et al. Post renal transplantation human herpesvirus 8-associated lymphoproliferative disorder and Kaposi's sarcoma. *Br J Haematol* 2001;113:425-8.
91. Mozzanica N, Cattaneo A, Fracchiolla N, et al. Posttransplantation cutaneous B-cell lymphoma with monoclonal Epstein-Barr virus infection, responding to acyclovir and reduction in immunosuppression. *J Heart Lung Transplant* 1997;16:964-8.
92. Tas S, Simonart T, Dargent J-L, et al. Granulomatose lymphomatoïde à localisation cutanée isolée après une transplantation cardio-pulmonaire. *Ann Dermatol Venerol* 2000;127:488-91.
93. Euvrard S, Pouteil Noble C, Kanitakis J, et al. Successive occurrence of T-cell and B-cell lymphomas after renal transplantation in a patient with multiple cutaneous squamous-cell carcinomas. *N Engl J Med* 1992; 327:1924-6.
94. Penn I. Sarcomas in organ allograft recipients. *Transplantation* 1995;60:1485-91.
95. Wehrli BM, Janzen DL, Shokeir O, Masri BA, Byrne SK, O'Connell JX. Epithelioid angiosarcoma arising in a surgically constructed arteriovenous fistula: a rare complication of chronic immunosuppression in the setting of renal transplantation. *Am J Surg Pathol* 1998;22:1154-9.
96. Kanitakis J, Euvrard S, Montazeri A, et al. Atypical fibroxanthoma in a renal graft recipient. *J Am Acad Dermatol* 1996;35:262-4.
97. Paquet P, Pierard G. Invasive atypical fibroxanthoma and eruptive actinic keratoses in a heart transplant recipient. *Dermatology* 1996;192:411-3.
98. Butt A, Roberts DL. Renal transplant recipients and protection from sun: need for education. *Lancet* 1997;349:179-80.
99. Cowen EW, Billingsley EM. Awareness of skin cancer by kidney transplant patients. *J Am Acad Dermatol* 1999;40:697-701.
100. Otley CC. Organization of a specialty clinic to optimize the care of organ transplant recipients at risk for skin cancer. *Dermatol Surg* 2000;26:709-12.

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