Invited Comment

Skin cancers after transplantation

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Renal transplantation has been performed for more than 35 years with a large success. However, the organ tolerance has to be associated with the induction and the maintenance of an immunosuppressive status in the patient which induces the development of skin cancers. Skin cancers are considered to be the most frequent tumours in transplant patients.

The incidence of skin cancer is increased in transplant recipients as compared to the general population and varies according to the country concerned. Thus, Hartevelt et al. [1] found a cumulative incidence of skin cancer, ranging from 10 to 40% at 10 and 20 years after transplantation. This incidence is higher in Australians, 45 and 70% at 10 and 20 years, respectively, after the transplantation. This fact is related to more intense sun exposure at these latitudes. Among the skin cancers, cutaneous premalignant and malignant epithelial lesions (carcinoma) are the most frequent skin tumours in organ transplant recipients [2-4].

Carcinoma

Two kinds of skin carcinomas may develop: basal-cell carcinoma and squamous-cell carcinoma. In the general population, basal-cell carcinomas are more frequently seen than squamous-cell carcinomas, but in the transplant population, the ratio of squamous-cell to basal-cell carcinoma in renal transplant recipients is greater than 1. More often, squamous-cell carcinomas develop from warts or actinic keratosis.

Premalignant cutaneous lesions

Warts. The two most frequent types are verrucae vulgares (Figure 1) and verrucae planae warts (Figure 2). Their frequency increases with the duration of immunosuppression with a mean of 15% at 1 year and 85% at 5 years in the literature. They are essentially localized on sun-exposed areas particularly the face (around the mouth) and the back of the hands. Their clinical features are similar to those found in non-immunosuppressed patients. The lesions are generally multiple. Data in the literature indicate that different types of HPV [5,6] can be found in these lesions. Types 1, 2, 3 and 4 are the most frequent but...
HPV 6/11 and HPV 16/18, which are potentially oncogenic and normally located in the mucosa of non-immunosuppressed patients, have been described in warts. The evolution of warts in transplant patients is characterized by a high frequency of recurrence and the development of squamous-cell carcinomas with the apparition of vegetating lesions on warts. Treatment of warts has to be provided as early as possible. It is evident that it is crucial to control that warts are absent in patients before transplantation and to provide early treatment once warts appear after transplantation. The treatment is essentially physical with liquid nitrogen, electrosurgery, and CO₂ laser. Surgery has to be avoided because of the risk of viral dissemination. When the lesions are profuse, treatments with local or oral retinoids (etretinate, isotretinoin) are indicated. More recently, Imiquimod has been introduced, which stimulates local production of interferon in the skin, and for resistant warts, injection of bleomycin or local application of nitrogen mustards has been proposed. Finally, physical treatment and local retinoids can be combined: in a first step, warts are destroyed by laser, electrosurgery, or liquid nitrogen, then topical retinoids are applied on the skin for several months.

Actinic keratosis (Figure 3). Their frequency is increased as compared to the general population, with a mean of 40% after 5 years of immunosuppression [7]. Similar to warts, they are located in uncovered areas and they are often associated with warts. The occurrence of an infiltration of the lesion and the rapid recurrence of the lesion are signs of transformation into a squamous-cell carcinoma. Similar to what is found in warts, different types of HPV may be found in association with actinic keratosis. For early lesions, electrosurgery or cryotherapy may be used. But, as soon as transformation into a squamous carcinoma is suspected, biopsy has to be performed followed by complete excision if the histology indicates transformation into squamous-cell carcinoma. In locally recurrent forms, long-term preventive treatment with topical retinoids should be considered in association with surgery or physical treatment. In diffusely spreading forms systemic administration of retinoids is a treatment option.

Squamous-cell carcinoma and basal-cell carcinoma

Clinical aspect. Squamous-cell carcinomas are almost exclusively localized on sun-exposed areas of the skin, whereas basal-cell carcinomas frequently develop on the trunk as well. Similar to what is seen with keratosis, the location of squamous-cell carcinomas depends on the age of the transplantated patient. Before 40 years, the majority of lesions are on the dorsum of the hands, the forearms and the trunk, whereas after 40 years, the majority of lesions develop on the head. The clinical aspect does not differ from that seen in the general population. The tumour appears as a cutaneous nodular lesion (Figures 4 and 5), which is infiltrating and develops ulceration or bleeding. The squamous-cell carcinoma often develops on warts or lesions of keratosis. In the latter case, the infiltrating character of the lesion is an important diagnostic point. Multiple carcinomas are also frequent and occur in more than 50% of transplanted patients with skin cancers.

Evolution. One specific point of these cutaneous carcinomas in transplant recipients is the evolution, which is usually more rapid than in the general population. Consequently, it is important to avoid a delay in the excision of the lesions. Relapses and metastases are more frequent that in the general population, the frequency ranging from 5 to 10%.

Histology. The histological features of squamous-cell carcinomas are usually those of an invasive or undifferentiated carcinoma. Transitional forms between the common wart and squamous-cell carcinoma have been reported making the diagnosis sometimes difficult for the pathologist. The histological features of basal-cell carcinomas in transplant recipients are similar to those of basal carcinomas in the general population.
Risk factors. Four main risk factors account for the high frequency and the aggressive evolution of these carcinomas.

(i) HPV types. The high prevalence of HPV DNA described in squamous-cell carcinomas and basal-cell carcinomas of these patients suggests a potential role of HPV in the aetiology of these lesions. As in warts, different types of HPV can be found [8] and more than one type of HPV may be identified in the same carcinoma. Other types of virus, mainly CMV have also been shown to be associated with HPV. The percentage of HPV-positive carcinomas ranges from 0 to 70% according to the studies. The discrepancies which are noted between the studies are probably related to differences in the technique used. The types of HPV most frequently encountered are 2, 5/8, 31/35 and 16/18 (Figure 6). Curiously, the rules of which type of HPV is oncogenic or not, that are valid in the general population, do not apply in carcinomas of transplant recipients. For example, HPV1 and 2, which are classically non-oncogenic, may be present in carcinomas of allograft recipients. Furthermore, HPV 6/11 and 16/18, which are located only on the mucosa in the non-transplanted patient, may be detected in carcinomas of the skin of the transplanted patient.

(ii) Immunological risk factors. Transplant recipients are under continuous immunosuppression with azathioprine, prednisone, cyclosporine and more recently FK 506. The risk of skin carcinoma increases with the duration of immunosuppression. However, currently it is not clear whether the risk is higher with some of these drugs, notably aziathioprine [9]. It seems that carcinogenic risk is more related to the degree of immunosuppression than to a specific immunosuppressive agent. Both natural killer cells, which are depressed in transplant recipients, and cytotoxic T cells, have a role in the control of proliferation of epithelial cells.

(iii) Exposure to sunlight. Exposure to sunlight is believed to be one of the most important risk factors for the development of both precarcinomatous and carcinomatous lesions. UV light causes DNA damage in keratinocytes and induces immunosuppression.

(iv) Genetic factors. The information on this point is not yet definite. An association between the class II antigen HLA-DR7 and the occurrence of skin cancers has been described. Conflicting results have been reported concerning HLA-A11: both negative and positive associations have been noted [10]. There is apparently a positive association between HLA B27 and skin cancer.

Treatment. The treatment of carcinomas is surgical excision with a minimal limit of 2 mm, which has to be increased to between 5 and 8 mm if it is a relapse, if the lesion is large, or if the evolution is rapid. Often the size of the excision necessary for carcinomas developing on warts or keratotic lesions is such that skin grafts are necessary. Lymph node metastases have to be treated by lymph node resection with radiotherapy. Systemic retinoids are a therapeutic option in selected patients who develop a great number of lesions over short periods. Protocols have yet to be developed,
however, to define the exact role of retinoids in the prevention of malignant lesions of transplant recipients. Studies [11–13] have been performed with topical retinoids using either 0.05% tretinoin or etretinate in low doses. These studies show an effect on keratosis with tretinoin and on carcinoma with combined treatment after 6 months. However, all these studies have been performed on small numbers of patients. The duration of the treatment remains to be determined. Intermittent treatment cycles have been proposed (3 or 6 months of tretinoin followed by 3 or 6 months without treatment). The tolerance is good, the irritation is generally mild and less pronounced than in immunocompetent patients. In any case, regular surveillance of the skin of transplant recipients is crucial. Suspicious lesions should be promptly biopsied. Keratoses and warts have to be treated. Because of the role of UV light, sun protection has to be used. The best protection is clothes, but sun screens can be used in addition, mainly on the face and the hands, but long exposure to sunlight should be avoided even with sun protection.

Finally, in patients with multiple skin cancers or more than two relapses, immunosuppressive therapy has to be reduced. In several patients, improved control of skin cancer has been noted thereafter [14].

### Cutaneous lymphomas

The incidence of cutaneous lymphoma is currently unknown. Only 10 cases have been reported in the literature. Six were cutaneous B lymphomas and four were cutaneous T lymphomas.

These nine lymphomas developed in men. The mean delay after transplantation was 5 years with a range between 0.5 and 11 years.

#### Cutaneous B-cell lymphoma

**Clinical aspect.** The cutaneous lesions are either single or multiple nodules on the skin which frequently ulcerate [14–18]. The skin lesions are isolated without any visceral involvement. B-cell lymphoma in the oral cavity has also been reported. The patients had erythematous or cyanotic hyperplastic gingival lesions. The infiltrate was composed of lympho-plasmocytoid cells with high mitotic activity. Infiltrating cells were EBV positive.

**Histology.** Histology shows a non epidermotropic infiltrate constituted of either blasts and small lymphocytes, or of mature lympho-plasmocytes. The B phenotype of tumour cells should be confirmed by immunohistochemistry, but atypical expression of CD30 antigen was seen in several cases (in general CD30+ cells are T cells).

**Treatment.** The treatment of choice is radiotherapy. Cutaneous relapse may occur, but visceral metastases have not been reported so far. It has not been proven that reduction of immunosuppressive treatment is effective.

#### Cutaneous T-cell lymphoma

**Clinical aspect.** The patients may present with erythrodermic [19] or haemorrhagic plaques on the legs [11]. One patient had a Sézary syndrome [20]. The histology is characterized by consistent epidermotropism similar to that seen in epidermotropic cutaneous T-cell lymphomas (mycosis fungoides and Sézary syndrome). EBV and HTLV-1 DNA have not been identified in the tumour cells.

**Treatment.** As in the case of epidermotropic lymphomas, the treatment options are corticosteroids, radiotherapy, nitrogen mustard or chemotherapy. In fact, the number of patients is too low to define a protocol. Finally, post-transplant cutaneous B-cell lymphomas seem to have the same prognosis as in the general population, while T-cell lymphomas follow a more aggressive course. EBV has only been identified in B-cell cutaneous lymphomas.

### Naevi and melanoma

#### Naevi

While an increase in skin carcinomas following transplantation is well established, surprisingly little information is currently available on the risk of melanoma. An increased number of benign naevi is found in children who have undergone renal transplantation. This increase is more pronounced in sites which are not chronically sun exposed including palms and hands [21]. Moreover, a strong correlation between the number of naevi and the duration of immunosuppression has been formed in paediatric renal transplant recipients independent of age [22]. Eruptive dysplastic naevi have been anecdotally reported in paediatric renal transplant recipients.

#### Melanoma (Figure 7)

Three situations can be encountered.

(i) Patients with melanoma prior to transplantation. There are only anecdotal reports on 31 patients [Cincinnati Transplant Tumour Registry (CTTR)] [23]. Nineteen percent died of recurrent disease. Unfortunately, the Breslow index in these cases is unknown and the follow-up time of the entire cohort was short. The prognosis of organ recipients previously treated for melanoma remains to be determined.

(ii) Melanoma developing after transplantation. At the moment, no single study has sufficient power to demonstrate an increased risk of melanoma following organ transplantation [24]. The data only suggest that there may be a moderate increased risk (2 to 10) after transplantation. The CTTR provides
data on 177 patients. Melanomas represent 14% of skin cancers in patients who received transplants in childhood compared to 5% in adults. So, the increase of naevi in children associated with the increase of melanomas suggests that immunosuppression begun at an early age may increase the risk of melanoma. The median time to develop melanoma after transplantation appears to be short, i.e. 46 months with a range of 1–244 months. Overall, 32% of all CTTR patients with melanoma during transplantation died.

(iii) Transmission of a melanoma from the donor. A donor with undiagnosed metastatic melanoma can give rise to the development of metastatic melanoma in the recipient. This outcome has been reported in 16 of 20 patients (CTTR) whose donor was found to have metastatic melanoma. Eleven of these 16 recipients died.

Histology. The histology is similar to those of melanomas of the general population. The treatment is similar to that in non-immunosuppressed patients, but obviously with the exception that interferon as an adjuvant therapy must be avoided.

Kaposi’s sarcoma

Epidemiology

Post-transplant Kaposi’s sarcoma affects the same populations that are susceptible to sporadic or endemic Kaposi’s sarcoma, i.e. patients of Mediterranean, black African or Caribbean origin.

The male/female ratio ranges from 2 to 40 with a male predominance similar to that found in other types of Kaposi’s sarcoma. The average time between transplantation and onset of Kaposi’s sarcoma is 20 months (2 months to 18 years). This delay is shorter after liver than after other organ transplantation. This fact could be related to the high prevalence of hepatitis B virus in patients with liver transplantation [25].

Clinical features

The cutaneous lesions are similar to classical Kaposi’s sarcoma and present as dark blue macules (Figure 8) which progress to plaques and sometimes to tumours. The localization is mucocutaneous in more than 90% of cases. On the skin, the lesions are mainly located on the trunk and the extremities, rarely on the face. Oral lesions are the most frequent mucous localization, predominantly located on the palate. Oedema is often associated and may even precede the skin lesions. The most frequent extracutaneous lesions concern lymph nodes, the gastrointestinal tract (mainly stomach and duodenum) and the lungs. These extracutaneous localizations are generally asymptomatic and are discovered during the staging. Pulmonary involvement is usually seen in the advanced stage of the illness. It is characterized by diffuse interstitial infiltrates, pulmonary nodules or pleural effusions.

Histology

Initially Kaposi’s sarcoma is characterized by proliferation of capillaries sprouting from normal vessels, and later by large vascular spaces in the dermis associated with proliferation of spindle cells.

Staging

Clinical examination has to include examination of ear, nose and throat, eyes and genitals. Chest involvement is detected by computed tomography complemented if necessary by bronchoscopy with bronchoalveolar lavage. Gastrointestinal involvement requires fibroscopy and colonoscopy (less frequent), involvement of deep lymph nodes requires thoracic and abdominal computed tomography. Human herpes virus type 8 (HHV8) can be detected by in situ PCR in tissue samples, specifically in mononuclear cells. Whether HHV8 is an aetiopathogenic factor or only an indicator of immunodeficiency is unknown. This must be clarified by prospective studies [26]. Detection of anti-HHV8 antibody levels is still a matter of clinical research.
After the global clinical check-up, Kaposi’s sarcoma can be staged. Al Khader et al. [27] distinguished: stage 1, localized skin lesions on one limb; stage 2, only skin lesions but localized on more than one limb; stage 3, single or multiple lymph nodes or visceral involvement; stage 4, any of the above stages with infection or other neoplasms.

**Treatment**

The treatment of Kaposi’s sarcoma in transplant patients is not well established. The main point on which everyone agrees, is reduction of immunosuppression to achieve the lowest possible drug concentrations [28]. However, immunosuppression may be vital for heart and liver transplants and this approach must be individualized, balancing risk and benefit after giving appropriate information to the patient.

In the Cincinnati cohort, in 17% of patients with mucocutaneous involvement and in 16% of the 143 patients with visceral involvement, disappearance of the lesions was noted only after immunosuppressive therapy had been reduced. Regression of the lesion may take several months. Whether treatment is necessary will depend on the type of lesions. For mucocutaneous lesions, cryotherapy, surgery, laser treatment, intra-lesional chemotherapy (bleomycin), or radiotherapy may be used. In stage 3, the most commonly used single chemotherapeutic agent is vinblastine at a weekly dose of 0.1 mg/kg for 5–10 weeks or bleomycin at a dose of 15 mg every 2 weeks. In more extensive forms, polychemotherapy can be tried, i.e. combinations of Adriamycin, bleomycin and vinblastine. Interferon alpha, which is often proposed for endemic Kaposi’s sarcoma, cannot be recommended because of the risk of inducing graft rejection. No effective antiviral drug is currently available. Recurrences of Kaposi’s sarcoma after retransplantation have been reported in all patients who had a history of sporadic or post-transplant Kaposi’s sarcoma which had disappeared. In view of this observation it may be necessary before retransplantation to measure anti-HHV8 antibodies in such patients to evaluate the risk of relapse.

**Rare skin cancers**

**Merkel cell carcinoma**

Merkel cell carcinoma is a rare malignant tumour of the skin. It is believed to originate from Merkel cells, which are presumably components of the amine precursor uptake and the decarboxylation system (APUD system). Merkel cell carcinoma is therefore presumably a neuroendocrine-derived neoplasia of the skin, but an epithelial origin cannot be excluded because of the presence of cytokeratin filaments in the tumour cells.

Several Merkel carcinomas have been described in transplant recipients [29]. The presentation of Merkel cell carcinoma is typically a firm erythematous nodule. It occurs on the extremities in over one-third of cases. In the transplant patient it appears to have an aggressive evolution with rapid growth and a fatal course. The treatment of the primary lesion is surgery with a free margin of at least 2 cm. Improved loco-regional control has been reported by several authors using post-operative irradiation to the primary site as well as to the regional draining lymph node. However, this has to be confirmed by further studies. For metastasis in Merkel cell carcinoma, chemotherapeutic agents may be used, cyclophosphamide 600 mg/m², methotrexate 40 mg/m², 5 fluorouracil 600 mg/m² and cis-platinum or etoposide. However, the response is generally poor. Furthermore, reduction or a discontinuation of immuno-suppressive drugs is advised in the hope to better control the cutaneous lesion.

**Vascular cutaneous tumour**

Angiosarcoma is an uncommon malignant tumour accounting for less than 1% of all sarcomas in the general population. Several cases of angiosarcoma have been reported in transplant patients in the literature but only one on the skin. Kibe et al. [30] reports the case of an angiosarcoma in a male 12 years after renal transplantation. This lesion was located on the scalp and characterized by multiple violaceous nodules surrounded by poorly demarcated red to purple discoloration. The treatment of this cutaneous tumour is similar to that performed in an immunocompetent patient, i.e. wide excision with 3 cm margins and possible post-operative radiotherapy. Histologically, the main differential diagnosis is Kaposi’s sarcoma.

**Mesenchymal cutaneous tumours**

**Dermatofibrosarcoma protuberans.** Lai et al. [31] reported the first case of a patient who developed a dermatofibrosarcoma only 4 years after renal transplantation. This soft tissue tumour is characterized by local recurrence, but only rarely by metastatic spread. A wide and deep excision (margins 3–5 cm) is necessary to prevent recurrence.

**Malignant fibrous histiocytoma.** A malignant fibrous histiocytoma has been noted in a long-term renal transplant [31] concomitantly with skin carcinoma and non-Hodgkin’s lymphoma.

**Adnexal gland carcinoma**

A syringomatous carcinoma has been described after kidney transplantation in one patient under cyclosporin [32]. Syringomatous carcinoma is an adnexal tumour derived from eccrine sweat glands. Its growth is slow but extremely invasive with a very high risk of local recurrence due to extensive peri-neural invasion.
Conclusion

In conclusion, the prophylaxis of skin cancers in graft recipients comprises skin protection, information to the patient about the risks of skin tumours and an early treatment of pre-cancerous skin lesions (keratosis, warts). Good cooperation between the specialists is necessary. All transplanted patients should have a dermatological examination at least once a year.

References