CASE REPORT

Excessive numbers of skin cancers and pre-malignant skin lesions in an Australian heart transplant recipient

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Abstract

One and a half years after heart transplantation an Australian man developed his first skin cancer. In the period until his death, 7 years after the transplantation, 34 histologically confirmed squamous cell carcinomas developed, 17 intra-epidermal carcinomas, and 9 basal cell carcinomas. Most skin cancers were confined to chronically sun exposed sites. Exposure to sunlight and human papillomavirus are important factors in the development of skin cancer in renal transplant recipients, and further studies are needed to establish the role of these risk factors in cardiac transplant recipients.

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Keywords: skin cancer; cardiac transplantation; human papillomavirus

It is well recognised that organ transplantation, with its associated immunosuppressive treatment, is complicated by an increased incidence of certain cancers.¹ Most data on the increased risk of squamous cell carcinomas and basal cell carcinomas refer to renal transplant recipients,²⁻⁴ and few data are available about the corresponding risk in other organ transplant recipients. We describe the case of an Australian patient in whom an excess of skin cancers and pre-malignant lesions developed, after heart transplantation.

Case report

A white man, born in Australia in 1932, underwent orthotopic heart transplantation in Sydney in August 1987 for ischaemic heart disease. His immunosuppression on discharge was cyclosporin (200 mg twice a day), prednisolone (12.5 mg twice a day), and azathioprine (25 mg twice a day). Shortly after the transplantation he also had an initial course of antithymocyte globulin. The dose of cyclosporin was gradually tapered to 75 mg twice a day and the dose of azathioprine was increased to 100 mg daily. The patient had skin type II and baldness.

One and a half years after the transplantation, in February 1989 his first skin cancer developed, and subsequently numerous squamous cell carcinomas, basal cell carcinomas and intra-epidermal carcinomas were surgically removed. Table 1 shows the histologically confirmed skin cancers and pre-malignant lesions. Most skin cancers were confined to chronically sun exposed sites (table 2). Additional clinically apparent intra-epithelial carcinomas and solar keratoses, not included in the tables, were treated with cryotherapy without histological diagnoses.

In August 1994, seven years after the transplantation, the patient died of pulmonary failure.

Discussion

This report shows that skin cancers can be an important problem in heart transplant recipients as well as in renal transplant recipients as previously established.²⁻⁵ For example, in a group of renal transplant recipients who received their transplant at University Hospital Leiden, the Netherlands, the cumulative inci-

Table 1 Numbers of skin cancers and pre-malignant lesions histologically diagnosed in an Australian heart transplant recipient

	1989	1990	1991	1992	1993	1994	Total
Squamous cell carcinoma	7	0	4	4	12	7	34
Intra-epidermal carcinoma	4	4	0	2	6	1	17
Basal cell carcinoma	3	1	0	3	2	0	9
Solar keratoses	3	2	1	2	2	1	11
Total neoplastic lesions	17	7	5	11	22	9	71

Table 2 Site of the skin cancers and pre-malignant lesions

Site	SCC	IEC	BCC	Sol K	Total
Scalp	9	2	0	1	12
Face	18	11	6	7	42
Neck	1	0	0	0	1
Back of hands	3	0	0	0	3
Forearm	0	1	1	1	3
Chronically sun exposed skin:					
Number of lesions	31	14	7	9	61
Absolute (%)*	91.1	82.4	77.8	81.8	85.9
Adjusted (%)†	98.0	95.7	94.3	95.5	96.7
Back	1	0	0	0	1
Chest	0	0	0	1	1
Shoulder	1	1	0	0	2
Limb	1	2	2	1	6
Irregularly sun exposed skin:					
Number of lesions	3	3	2	2	10
Absolute (%)*	8.9	17.6	22.2	18.2	14.1
Adjusted (%)†	2.0	4.3	5.7	4.5	3.3
Total	34	17	9	11	71

SCC, squamous cell carcinoma; IEC, intra-epidermal carcinoma; BCC basal cell carcinoma; Sol K, solar keratosis.

*Percentage of the absolute numbers of skin cancers and pre-malignant lesions.

†Percentage adjusted for the surface of chronically sun exposed skin (17.4% of body surface) and irregularly sun exposed skin (82.6% of body surface).

dence of non-melanoma skin cancer increased from 10% after 10 years to 40% after 20 years of graft survival.⁵ In Australia, where the population is exposed to a much higher level of ultraviolet radiation, the cumulative incidence of non-melanoma skin cancer had reached 40% after 10 years.² Squamous cell carcinomas are said to be more aggressive in renal transplant recipients than in the general population,³ and they seem to be associated with a higher risk of metastasis in such patients.³

In addition to immunosuppressive treatment, exposure to sunlight is believed to be one of the most important risk factors for the development of both non-melanoma skin cancers and warts in renal transplant recipients.^{3,4,6} This seems likely to be true of our heart transplant recipient too, because almost all his skin cancers occurred on chronically sun exposed sites. This suggests that immunosuppression influenced a later stage of carcinogenesis where epidermal cells had been irradiated. That is, ultraviolet light exerts its harmful effect both by inducing DNA damage and possibly by inducing immunological unresponsiveness⁷ in concert with immunosuppressive agents.

Several specific immunological and immunogenetic factors may have a role in the development of non-melanoma skin cancer in renal transplant recipients.⁴ These factors may influence other transplant recipients as well. HLA-A11 is negatively and HLA-B27 positively associated with the development of skin cancer.^{8,9} In addition, long-term antigenic stimulation by a poorly matched graft is thought to induce skin cancer.¹⁰ HLA-B mismatching was associated with a significantly increased risk of squamous cell carcinoma in renal transplant recipients.⁴

There is epidemiological and serological evidence that human papillomaviruses lead to the development of squamous cell carcinomas in transplant recipients.^{3,4,6,11} The number of warts a patient develops is strongly associated with the development of non-melanoma skin cancer,^{3,4,6} and the risk of skin cancer is higher in patients without an apparent class switch from IgM to IgG in response to the fusion protein of the late antigen (L1) of human papillomavirus type 8 and β -galactosidase than in patients with a good humoral response to this fusion protein.¹¹ Moreover, in transplant recipients, the nucleotide sequences of human papillomaviruses are often found in squamous cell carcinomas.^{12,13} Recently, we detected human papillomavirus DNA in 48 (80%) of 60 cases of squamous cell carcinoma using a nested PCR approach.¹⁴ Typing by direct sequencing showed human papillomavirus types that are associated with epidermodysplasia verruciformis.

Because of the strong associations between chronic sun exposure and the risk of non-melanoma skin cancer in the present case as well as in previous studies, transplant recipients should be encouraged to wear long sleeves, long trousers, and a hat outdoors, especially in sunny climates. Though regular use of sunscreens may have some effect in slowing the development of solar keratoses in the non-immunosuppressed population,¹⁵ the

extent of the protection it gives against cancer remains uncertain. Indeed it has been suggested that the use of sunscreens, which are known to reduce sunburn but which may be less effective in preventing local immunosuppression,^{16,17} gives a false feeling of safety. Perhaps it would be better to warn transplant patients to avoid the midday sun, when the ultraviolet B radiation is most intense.

We advise regular surveillance of transplant recipients with skin problems and easy access of all patients to a dermatologist, as well as early biopsy of suspicious lesions. This facilitates early removal of malignant and premalignant lesions to reduce the risk of skin cancer and metastasis.

Recent studies have suggested that etretinate (Tigason) or its main metabolite acitretin (Neotigason) is effective in the treatment of solar keratoses in renal transplant recipients.^{18,19} Most patients also experienced a considerable reduction of new squamous cell carcinomas during treatment.^{18,19} Despite concern about possible allograft rejection associated with the immunopotentiating effects of etretinate,²⁰ no such side effects have yet been described. Further studies are clearly needed to establish whether retinoids reduce solar keratoses and prevent non-melanoma skin cancer, both in renal-transplant recipients and in recipients of heart or other organs.

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SHORT CASES IN CARDIOLOGY

Direct evidence of patent foramen ovale as a route for paradoxical embolism

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A 83 year old woman was transferred from the department of surgery because of a syncopal attack with hypotension. Twenty days before she had had a palliative operation for gall bladder adenocarcinoma with hepatic invasion. Some days later she had had an ischaemic stroke in the middle cerebral artery territory, which was confirmed by computed tomography. Carotid ultrasonography showed no stenoses. Despite these clinical events and prolonged immobilisation, she could be treated only with low-dose subcutaneous heparin because of postoperative gastric

haemorrhage which required blood transfusions. Transthoracic echocardiography (TTE) showed a thrombus abutting the tricuspid valve and crossing a patent foramen ovale to reach the left atrium and mitral valve (figure). A Doppler estimate of right ventricular systolic pressure was about 75 mm Hg.

A patent foramen ovale is a risk factor for ischaemic stroke¹; indirect evidence of its role as a route for paradoxical embolism through a right-to-left shunt stems from case-control studies.^{2,3} A direct role is difficult to demonstrate,⁴ because diagnosis of paradoxical embolism is based upon indirect criteria,⁵ and documentation of a patent foramen ovale itself usually requires transesophageal echocardiography, with intravenous saline contrast when necessary.¹

This patient had several risk factors for deep vein thrombosis, such as old age, adenocarcinoma, recent surgery, and prolonged immobilisation: but she also had contraindications to antithrombotic therapy.⁶ The shape of the thrombus indicated a venous genesis. Pulmonary hypertension probably forced open the foramen ovale,⁵ leading to an interatrial shunt. The thrombus across the interatrial septum may explain the ischaemic stroke and confirm the role of patent foramen ovale in paradoxical embolism, especially in the presence of pulmonary hypertension.

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Transthoracic echocardiogram (modified right ventricular inflow tract view, diastolic frame) showing the thrombus (THR, arrows) abutting the tricuspid valve (TV) and crossing the interatrial septum at the level of foramen ovale to impinge on the mitral valve (MV). RV, right ventricle; LV, left ventricle; RA, right atrium; LA, left atrium.

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