Skin cancers in renal transplant recipients: a description of the renal transplant cohort in Bern

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Summary

Background/aims: Skin tumours, in particular squamous-cell carcinomas (SCC), are the most common malignant conditions developing in transplant recipients. The aim of this study is to investigate the frequency and type of skin cancer in patients receiving immunosuppressive therapy after organ transplantation.

Methods: Multivariate logistic regression analysis was performed on data of 243 renal transplant patients who attended the dermatology outpatient clinic for the first time after transplantation in the period January 2002–October 2005.

Results: We found an increased risk of actinic keratosis (AK) and SCC in renal transplant recipients with a basal cell carcinoma (BCC) / SCC ratio of 1:7. Older patients had AK more frequently (odds ratio [OR] 1.11, 95% confidence interval [CI] 1.06–1.15; $p < 0.0001$) and SCC (OR 1.14, CI 1.07–1.22; $p < 0.0001$) than younger patients. Men had AK (OR 0.19, CI 0.08–0.45; $p = 0.0002$) and SCC (OR 0.25, CI 0.07–0.89; $p = 0.0332$) more frequently than women. The duration of immunosuppressive therapy correlated significantly with the numbers of AKs (OR 1.15, CI 1.08–1.24; $p < 0.0001$) and SCCs (OR 1.16, CI 1.05–1.28; $p = 0.0025$), and patients with fair skin had more AKs (OR 0.31, CI 0.14–1.24; $p < 0.0001$) and SCCs (OR 0.11, CI 0.02–0.52; $p = 0.0054$) than darker skinned patients. We could not identify any specific immunosuppressive drug as a distinct risk factor for AK or non-melanoma skin cancer (NMSC).

Conclusion: Skin cancers are increased in the renal transplant population. Main risk factors for skin cancers are fair skin type and long duration of immunosuppressive therapy. A follow-up programme is necessary for early detection of skin cancer and precancerous conditions. Preventive strategies should include specialist dermatological monitoring and self-examination.

Key words: immunosuppression; preventive strategies; regular follow-up; risk factors; skin cancer

Introduction

Renal transplantation is a procedure frequently adopted in the treatment of renal failure which requires, in addition to appropriate surgical techniques, life-long immunosuppressive therapy. More than one million people worldwide carry organ transplants, of which solid kidney transplants represent the majority [1]. Patients' survival time has steadily lengthened in recent decades as a result of an optimised immunosuppressive regimen preventing transplant rejection, improved treatment of infections and the preferred use of human leukocyte antigen (HLA)-matched kidneys from deceased donors [2–4]. However, one consequence of long-term immunosuppressive therapy is facing dermatologists with increasing numbers of skin cancers in these patients. Follow-up programmes including preventive and surveillance strategies are needed [2, 3]. Ultraviolet radiation represents the major risk factor, as skin tumours appear more frequently in countries with high sun exposure (e.g. Australia) [5] and in sun-exposed areas in patients with a fair skin type. Furthermore, biopsies of squamous cell carcinomas often show features of human papillomavirus infection (HPV), since HPV may also be considered carcinogenic [6]. However, a recent study analysing serological data could not define HPV infections as aetiological factors for SCCs in transplant recipients [7]. The excess of skin cancer in immunosuppressed patients has been attributed to two main pathomechanisms: first, a direct carcinogenic action of these agents [8, 9], and second, impaired eradication of precancerous changes due to permanent immunosuppression [10, 11]. The risk of both systemic cancer and skin cancer in patients who underwent

transplantation is 3–4 times higher than in the general population [12]. Skin cancer represents the majority. In Australia some 45% of patients developed skin cancer within 10 years of transplantation [5, 13]. European studies from Ireland, the Netherlands, the UK and Italy reported an incidence of 10–15% [14–17]. Studies from Japan showed a lower incidence [18, 19]. Compared to age- and sex-matched control populations the population-based standardised incidence ratio of skin cancer is increased 65–82-fold for squamous cell carcinomas (SCC), 10-fold for basal cell carcinomas (BCC) and 3.4-fold for melanoma (MM) in organ transplant recipients [14, 15, 20]. The incidence of Kaposi's sarcoma, which has been related to viral infection, is increased even 84-fold due to immunosuppression in transplant recipients [21–23].

The aim of this study is to investigate the frequency and type of skin cancer as well as to define risk factors for skin cancer in patients receiving immunosuppressive therapy after kidney transplantation. Since there is evidence that certain immunosuppressive substances such as azathioprine [11] have a greater impact on carcinogenesis, we correlated the immunosuppressive regimens with the type and numbers of skin cancer lesions.

Material and methods

Patients

The research was conducted in full compliance with ethical principles, including the provisions of the World Medical Association Declaration of Helsinki 2000.

In accordance with internal guidelines of the University of Bern we collected the data of 243 renal transplant recipients in the period January 2002–October 2005 who were on regular follow-up at our hospital. To optimize follow-up of transplant recipients we installed a special dermatological consultation unit at the department of nephrology. This enabled close follow-up of all transplanted patients during their routine nephrological controls at the department of nephrology. Prior to kidney transplantation all patients had been checked by a dermatologist for skin cancers and/or premalignant conditions and treated for evident lesions.

Clinical parameters

A detailed medical history was recorded and the entire skin of each patient was examined. All clinically evident skin lesions suspect for actinic keratoses (AK), squamous cell carcinoma (SCC), basal cell carcinoma (BCC) or malignant melanoma (MM) were recorded. If the lesion was clinically clearly recognised as AK, treatment was performed without histological confirmation. In all other cases a punch biopsy was evaluated histologically for non-melanocytic lesions and an excision biopsy for lesions suspect for MM.

Statistical analysis

Two multivariate logistic regression models were applied to investigate the influence of immunosuppressive medication, the duration of treatment, age, sex, and skin type on the incidence of AKs and SCCs respectively. A p-value of <0.05 was considered statistically significant and no correction was done for multiple testing.

Results

Patients

The patients' characteristics are listed in table 1. 243 patients, 154 males (63%) and 89 females (37%), with a mean age of 50.7 years (±13.0, range 19–79) were included in the study. The mean duration of immunosuppression was 9.2 years (±7.3, range <1–34). In general the patients were treated by a combination of immunosuppressive drugs (mean 2.5 drugs, ± 0.6). The majority of patients presented skin types II and III in the Fitzpatrick classification (in 23 patients the skin type was not determined). These patients received various immunosuppressive regimens with a total of 22 different combinations of immunosuppressive medication ranging from monotherapy with cyclosporine to four-drug combination regimen (table 2). To demonstrate the relation of length of immunosuppression to the frequency of skin cancer the patients were assigned to one of five different groups (0–5 yrs, 6–10 yrs, 11–15yrs, 16–20 yrs, >20 yrs) as shown in figure 1.

Increased risk of AK and SCC in renal transplant patients

In 243 patients who underwent systematic examination for skin cancer before and after transplantation we observed a total of 541 AKs and 158 non-melanoma skin cancer (NMSC) (138 SCC, 20 BCC) and 2 malignant melanomas. This results in a BCC to SCC ratio of 1:7. Over time, with the increasing duration of immunosuppression, the number of diagnosed SCC exceeded the number of BCC to an increasingly large extent. Within the first 10 years the incidence of NMSC (SCC and BCC) was 17.8%.

Risk factors for skin cancer

To investigate the distinct clinical parameters influencing the occurrence of AK, BCC, SCC or MM in renal transplant patients, we performed multivariate logistic regression analysis. We found a relationship between the incidence of skin cancers and the clinical parameters such as patients' age, sex and skin type, as well as time period after transplantation, which is identical to the duration of immunosuppressive treatment (fig. 1). Elderly patients had

AK more frequently (odds ratio [OR] 1.11, 95% confidence interval [CI] 1.06–1.15; p <0.0001) and SCC (OR 1.14, CI 1.07–1.22; p <0.0001) than younger patients. Men had AK (OR 0.19, CI 0.08–0.45; p = 0.0002) and SCC (OR 0.25, CI 0.07–0.89; p = 0.0332) more frequently than women. As suspected, the duration of immunosuppressive therapy correlated significantly with the numbers of AKs (OR 1.15, CI 1.08–1.24; p <0.0001) and SCCs (OR 1.16, CI 1.05–1.28; p = 0.0025), and patients with fair skin had more AKs (OR 0.31, CI 0.14–1.24; p <0.0001) and SCCs (OR 0.11, CI 0.02–0.52; p = 0.0054) than darker skinned patients. We observed a sharp increase in AKs and SCCs over time. In patients with more than 10 years' immunosuppression the frequency of AKs was 41.0% and of SCCs 7.6%. In the group with >20 years' immunosuppression more than 70% of the patients presented AK and 39% SCC.

Table 3 shows the effect of different parameters on the risk of developing AK and SCC. A highly significant effect is seen for the parameters age, duration of immunosuppression (years after transplantation) and skin type. A significant effect is seen for gender as an independent risk factor and the immunosuppressive drug prednisone. This means that the risk of developing AK and SCC increases in patients with higher age, fair skin and long-term immunosuppressive therapy. Also, the risk is higher in males than in females.

The effect of different types of immunosuppressive agents

Azathioprine was reported to have a main impact on skin tumour development [11]. We therefore investigated whether the substances used for immunosuppression had any effect on the development of AKs and skin cancers. The type of immunosuppression did not affect the development of AK and SCC. Only for prednisone (p = 0.027) was a statistically significant risk of developing AK shown. We could not identify azathioprine as high risk treatment for the development of AK or NMSC.

Discussion

This study investigates the frequency and type of skin cancer in renal transplant patients detected by a dermatologist for the first time after transplantation. All patients had a dermatological checkup before transplantation. No skin cancers were detected at this initial visit. The incidence of 17.8% for NMSC (SCC and BCC) within the first 10 years of immunosuppression is consistent with data from previous studies [14–17, 20].

In the normal population the incidence in Switzerland is some 23/100 000 for SCC and some 71/100 000 for BCC [24] resulting in 94 NMSC per 100 000 inhabitants. In our study only 243 patients developed 158 NMSC. Although this is a several-fold increase in incidence, we cannot rule out the possibility that at least some NMSC are not related to the immunosuppression.

Over time, most renal transplant patients developed actinic keratoses. Over 70% of the patients transplanted more than 20 years ago presented AKs. Although the number of these patients was small, this observation demonstrates the high risk of developing AKs and later SCC, since in renal transplant patients a high incidence of SCC has been demonstrated. In contrast to the general population, renal transplant patients present more SCC than BCC, i.e., the ratio of SCC to BCC in these recipients is reversed compared to the general population [25, 26]. In our patients we found a BCC to SCC ratio of 1:7, which is comparable to that reported in other studies [5] and the reverse of the ratio seen in the general population where BCCs are more frequent than SCCs [24]. Interestingly, the increase in SCC was much more rapid than the increase in BCC, as has been observed earlier [27]. As a consequence of these observations, renal transplant patients should undergo regular follow-up including skin examination. We would propose a dermatological checkup annually or every 3–6 months in patients with previous AKs and/or skin cancer.

In accordance with published data [28] the results of this study clearly demonstrate that the main reason for the increasing number of AKs and NMSC after transplantation is immunosuppressive therapy, which is imperative for these patients. The duration of immunosuppression correlates highly significantly with the numbers of patients affected by NMSC. In addition, elderly patients, men, and patients with a fair skin were found to be at higher risk of developing AKs and SCCs. The large relative and absolute number of patients with SCC suggests that immunosuppressive therapy promotes the development of AKs and SCCs. Precancerous lesions such as AKs tend to develop into SCC more often and more rapidly in renal transplant patients. Although our data suggest that the risk factors fair skin type, age, long-standing immunosuppressive therapy and male gender are associated with the development of skin cancer, they may not prove it. Nevertheless, it seems important to detect AKs at an early stage and to treat them. If AK and NMSC are diagnosed at an early stage, various minimal or non-invasive methods such as cryotherapy, photodynamic therapy and topical imiquimod or 5-fluorouracil can be used.

It has recently been demontrated *in vitro* that azathioprine induces chronic oxidative stress by forming reactive oxygen species (ROS) causing mutagenic damage of the DNA [11]. This observation may be one explanation for the increased prevalence of skin cancer in long-term survivors after organ transplantation. Although azathioprine has been shown to induce mutagenic oxidative DNA damage with UVA light [11], we could not identify azathioprine or any other specific immunosuppressive drug as a distinct risk factor for the development of AK or NMSC. Surprisingly, there was a small but significant increase in the risk of developing AK in patients treated with prednisone. This finding may be explained by the fact that prednisone is frequently given to patients with a higher load of immunosuppression, as for example to patients with poor graft function.

We also recorded a slightly higher incidence of AK development under the calcineurin inhibitor tacrolimus. Although the immunosuppression drug sirolimus, a mammalian target-of-rapamycin inhibitor (mTOR), has been reported to be associated with a lower incidence of de novo skin cancer [29], we could not demonstrate this effect. However, it has to be emphasised that the numbers in both the tacrolimus and sirolimus groups were too low to allow statistically significant statements.

The main limitation of this study is that we analysed a relatively small number of patients and that there is no matched control population. Furthermore, the study population was selected, as only patients seen at our hospital were included. The results may be influenced by centre-effects and may, therefore, not be applicable to other populations. Further studies are required to assess the exact relationship between immunosuppressive drugs and the development of skin cancer.

Because of the high risk of developing skin cancer there is a need to develop effective programmes for prevention, early detection, and therapeutic intervention. Guidelines for the follow-up of these patients have recently been published [30].

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Table 1

Patients' characteristics.

Patients	243
Male / female	154 / 89
Age (years, mean ± SD)	50.69 (±12.98), Range 19–79
Duration of immunosuppression (years)	9.24 (±7.32)+ Range 0–34
Number of immunosuppressive drugs	2.52 (±0.59) + Range 1–4
Skin type	I: 3, II: 149, III: 60, IV: 5, V:3 not determined: 23

Table 2

Regimens of immunosuppressive therapy.

Immunosuppressive regimen							
Monotherapy		Combination					
Substance	Patients (n = 7)	2 Substances	Patients (n = 107)	3 Substances	Patients (n = 124)	4 Substances	Patients (n = 5)
C	7	A T	1	A C P	71	A C M P	2
		A C	6	A P S	1	A C P S	2
		A P	20	A P T	3	C M P S	1
		C M	4	C M P	42		
		C P	70	C P S	3		
		M P	1	M P S	2		
		M S	1	M P T	1		
		M T	1	P S T	1		
		P S	2				
		P T	1				

Abbreviations: P: prednisone, C: cyclosporine, A: azathioprine, M: mycophenolate,

S: sirolimus, T: tacrolimus

Table 3

Effects of age, sex, duration of immunosuppressive therapy, regimens of immunosuppressive therapy on the occurrence of actinic keratoses (A) and squamous cell carcinomas (B). * p <0.05, statistically significant; ** p <0.01, highly significant; [1] β: beta coefficient; [2] SE: standard error; [3] PE: point estimate; [4] 95% Wald confidence limits

A

Clinical parameter			Odds ratio estimates				
	β^{1}	SE^{2}	PE^{3}	95% Limits[4]		P value	Significance
Age	0.100	0.020	1.11	1.06	1.15	<0.0001	**
Sex (male)	– 0.824	0.218	0.19	0.08	0.45	0.0002	**
Duration of immunosuppressive therapy	0.143	0.036	1.15	1.08	1.24	<0.0001	**
Skin type	– 1.184	0.396	0.31	0.14	0.66	0.0027	**
Immunosuppressive drugs:							
Prednisone	1.728	0.781	5.63	1.22	26.03	0.0270	*
Cyclosporine	0.471	0.691	1.60	0.41	6.20	0.4959	
Azathioprine	– 0.174	0.422	0.84	0.37	1.92	0.6803	
Mycophenolate	– 0.020	0.562	0.98	0.33	2.95	0.9712	
Sirolimus	0.352	1.379	1.42	0.10	21.20	0.7986	
Tacrolimus	1.975	1.228	7.20	0.65	79.98	0.1079	

B

| Clinical parameter			Odds ratio estimates				
	β^1	SE^2	PE^3	95% Limit[4]s		P value	Signifi-cance
Age	0.134	0.034	1.14	1.07	1.22	<0.0001	**
Sex (male)	− 0.702	0.329	0.25	0.07	0.89	0.0332	**
Duration of immunosuppressive therapy	0.150	0.050	1.16	1.05	1.28	0.0025	**
Skin type	− 2.189	0.787	0.11	0.02	0.52	0.0054	**
Immunosuppressive drugs:							
Prednisone	1.101	1.167	3.01	0.31	29.61	0.3452	
Cyclosporine	0.707	0.947	2.03	0.32	12.98	0.4557	
Azathioprine	0.600	0.653	1.82	0.51	6.56	0.3589	
Mycophenolate	− 0.192	1.184	0.83	0.08	8.38	0.8713	
Sirolimus	− 10.94	436.0	<0.001	<0.001	>999	0.9800	
Tacrolimus	− 10.51	553.1	<0.001	<0.001	>999	0.9848	
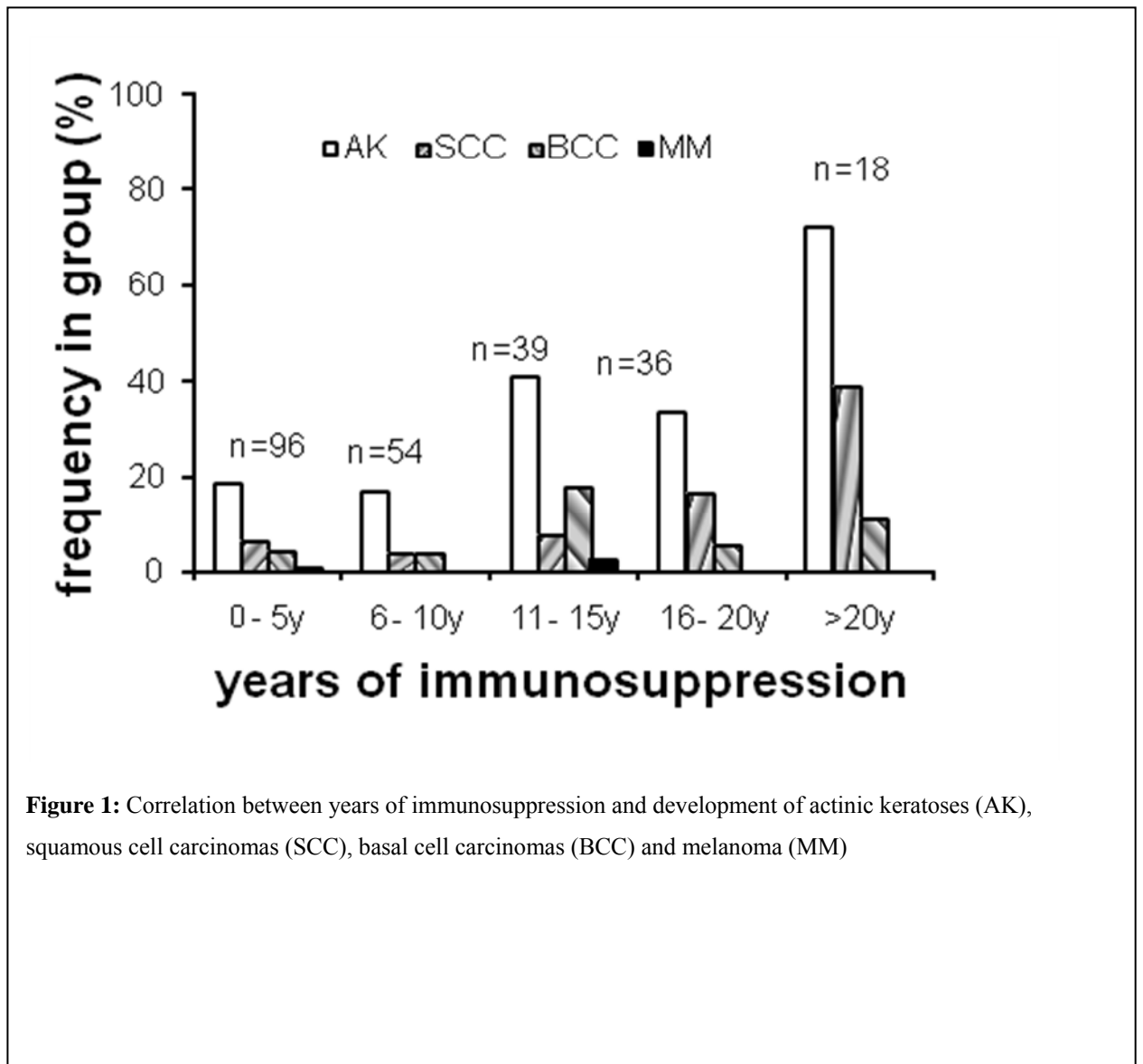
Figure 1: Correlation between years of immunosuppression and development of actinic keratoses (AK), squamous cell carcinomas (SCC), basal cell carcinomas (BCC) and melanoma (MM)