Basal Cell Carcinomas Developing in Solid Organ Transplant Recipients

Clinicopathologic Study of 176 Cases

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Objective: To assess the clinicopathologic features of basal cell carcinomas developing in organ transplant recipients.

Design: Case series.

Setting: University department of dermatology.

Patients: One hundred forty-six (7.2%) of 2029 transplant recipients followed up in our department who developed 176 histologically proven basal cell carcinomas. One hundred fifty-three random samples of basal cell carcinomas excised from nonimmunosuppressed patients served as controls.

Main Outcome Measures: Clinical data were gathered from the medical records. Histologic slides were retrospectively reexamined.

Results: Basal cell carcinomas developed an average of 6.9 years after transplantation, sooner after heart than kidney transplantation, and showed a relative predilection for heart allograft recipients. The mean age of transplant recipients with basal cell carcinomas was significantly lower than that of controls (54.6 vs 69.8 years), especially for recipients of renal transplants, and a male preponderance was found (male-female ratio, 4.8:1 vs 1.3:1). In both groups, basal cell carcinomas were predominantly found on the head and neck, but extracephalic locations were significantly more frequent in transplant recipients (37.5%) than controls (24.5%). Histologically, superficial basal cell carcinomas were more frequent in transplant recipients than controls (33.6% vs 14.4%). The density of the peritumoral cell infiltrate was lower in tumors from transplant recipients compared with controls. The tumor thickness and the presence of epidermal ulceration did not differ significantly between the 2 groups.

Conclusions: Basal cell carcinomas in transplant recipients show some clinicopathologic differences from their “ordinary” counterparts, namely, a younger age at development, male preponderance, more frequent distribution in extracephalic sites, and higher frequency of superficial subtypes.

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ORGAN TRANSPLANT recipients (OTRs) are at increased risk for developing various cancers, including skin cancers. Premalignant and malignant cutaneous tumors, including basal cell carcinomas (BCCs) and squamous cell carcinomas (SCCs), account for the most common malignancies developing in OTRs as a result of chronic immunosuppression, light exposure, and possibly also human papillomavirus infection. These tumors affect up to 40% of OTRs within 20 years after transplantation and are responsible for a mortality rate of 5% to 8%. The SCCs show the highest increase in incidence (×100) compared with the population at large. The incidence of BCC, the most common malignancy in humans, is also reportedly increased in OTRs, although to a lesser extent (×10) ; accordingly, the BCC/SCC ratio, which approximates 4 to 5:1 in control populations, has been found in most studies to be reversed in OTRs. So far, no detailed study has specifically dealt with BCC developing in OTRs. The present study was undertaken to obtain further insight into the clinicopathologic features of BCC developing in OTRs, and to search for specific features that differentiate it from BCC developing in ethnically matched nonimmunosuppressed patients.

METHODS

During the past 20 years, 2029 adult and pediatric recipients of solid organ allografts (kidney, heart, liver, and lung) were followed up in our department. Sixty-eight percent of these patients were men. The files of the patients were reviewed, and OTRs with at least one histo-
logically proven BCC were selected. The following clinical information was gathered from the medical records: organ grafted, interval between transplantation and (first) BCC development, age at BCC excision, and BCC location. The available histologic slides were retrieved and reexamined retrospectively, and the following features were assessed in a blinded fashion: histologic subtype of BCC (superficial, sclerodermiform, nodular or other), presence of epidermal ulceration (defined as absence of epidermis over the tumor), tumor (Breslow) thickness in millimeters (measured microscopically with an ocular grid at a magnification of ×100), and density of the peritumoral inflammatory cell infiltrate, scored semiquantitatively as 1 (absent or mild), 2 (moderate), or 3 (dense).

The group of control tumors comprised 153 BCCs retrieved randomly from the files of our dermatopathology laboratory. These had been excised in our department from 141 nonimmunosuppressed patients within 1 year, included in the follow-up period of the OTRs. The same clinicopathologic data for the OTRs were recorded for control patients and tumors. Statistical comparison was performed with the χ² test for qualitative data (sex ratio, distribution of organ grafts among OTRs with and without BCC, anatomic distribution of BCC, histologic subtypes, ulceration, and density of the peritumoral inflammatory cell infiltrate) and the unpaired t test for quantitative data (age, interval from transplantation to tumor appearance, and BCC thickness), with the threshold of P < .05 considered significant.

### RESULTS

#### CLINICAL FEATURES

Of the 2029 OTRs, 146 (7.2%) developed a total of 176 histologically proven BCCs. Of the 146 OTRs with BCC, 82.6% were men, and more than 20% of all patients had more than 1 BCC. The distribution of patients according to the allografted organ is given in Table 1. During the same period, 600 SCCs were also diagnosed in the same patient group (SCC/BCC ratio, 3.4:1). The main epidemiologic data from OTRs and control patients with BCC are given in Table 2 and Table 3. The male-female ratio was significantly higher in OTRs with BCC than controls. The mean age of OTRs with BCC was significantly lower (on average by 15 years) than that of controls (P < .001). This difference was even more pronounced for kidney (17 years) compared with heart (11 years) allograft recipients. Among OTRs with BCC, heart transplant recipients were on average significantly older than kidney and liver transplant recipients, at the time of both transplantation and BCC diagnosis (P < .001). The OTRs with BCC had developed BCC an average of 6.9 years after transplantation, sooner after cardiac than after renal transplantation (5.7 years vs 8.1 years; P < .01). The anatomic distribution of BCC in OTRs and controls is detailed in Table 4. Although in both groups BCC developed predominantly over the head and neck, a significantly higher percentage of OTRs with BCC (37.5% vs 24.5%) had the BCC develop in sun-protected (extracerebral) sites; furthermore, some unusual locations (such as auditory canal, genitalia, hand, wrist, and axilla) were noted in OTRs but not in controls.

#### HISTOPATHOLOGIC FEATURES

The main histopathologic features of BCC in OTRs and controls are given in Table 5 and Table 6. Compared with controls, BCCs in OTRs on average were thinner and more often ulcerated, but these differences did not reach statistical significance. No significant differences were noted in invasion of underlying structures, nerves, and cartilage. However, the two groups differed as to their histologic subtypes; BCCs in OTRs were more frequently (33.6% vs 14.4%; P < .001) of superficial subtype. The density of the peritumoral inflammatory cell infiltrate was significantly (P < .001) lower in OTRs than controls. When the anatomic distribution of BCC according to histologic subtype was considered, nodular BCCs predominated on the head and neck (83.2%), whereas superficial BCCs predominated on extracerebral sites (67.2%), mainly the trunk (49.3%).

Although the incidence of BCC, the most common human malignancy, is increased in OTRs compared with the general population, little specific attention has been paid to this tumor in the setting of organ transplantation. In some large series dealing with malignant tumors in OTRs, BCCs are collectively referred to, along with SCCs, as “nonmelanoma skin cancers,” and in some large cancer registries, BCCs are not reported at all. Therefore, data concerning these tumors may be flawed.

In this large series, 7.2% of OTRs developed at least 1 BCC. This incidence is likely to be underestimated, since some BCCs may be destroyed by family physicians without histologic confirmation, especially because many of these BCCs belong to the superficial subtype that is amenable to nonsurgical treatment (such as cryotherapy, electrocautery, local cytostatics, or immune modifiers). We found a 3.4-fold lower incidence for BCC than for SCC, the most common tumor developing in OTR. This finding is in keeping with most studies in the literature, which—with few exceptions—have reported an SCC/BCC ratio varying from 1.2 to 15:1. The organ grafted might have an influence on the SCC/BCC ratio. We have previously reported that heart transplant recipients tend to develop proportionally more BCC than SCC compared with kidney transplant patients. Our present findings further support this tendency, since heart transplant recipients with BCC accounted for 32.2% of all OTRs with BCC, contrasting with the fact that heart transplant recipients accounted for only 17.1% of the total OTR population. On average, our heart transplant recipients were older than kid-

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Table 1. Organ-Grift Distribution in the Total OTR Population and in OTRs With BCC

<table>
<thead>
<tr>
<th>Organ Grafted</th>
<th>Total OTRs, % (N = 2029)</th>
<th>OTRs With BCC, % (n = 146)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kidney</td>
<td>73.7</td>
<td>63.7*</td>
</tr>
<tr>
<td>Heart</td>
<td>17.1</td>
<td>32.2</td>
</tr>
<tr>
<td>Liver</td>
<td>6.4</td>
<td>2.8</td>
</tr>
<tr>
<td>Lung</td>
<td>2.9</td>
<td>0.7</td>
</tr>
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Abbreviations: BCC, basal cell carcinoma; OTR, organ transplant recipient. *P < .001.
ney and liver transplant recipients, both at the time of transplantation and at the time of (first) BCC diagnosis, but whether this difference may have favored the development of BCC in the former group is uncertain. On the other hand, considering that the incidence of SCC increases exponentially with time after transplantation and that of BCC in a linear fashion, the SCC/BCC ratio is expected to increase with time after transplantation within the same patient group. This fact likely explains the finding in a short follow-up study of OTRs that BCCs outnumbered SCCs, although this hypothesis has been disputed.

Our study shows that BCCs developing in OTRs show some significant differences compared with their "ordinary" counterparts appearing in nonimmunosuppressed patients. On average, BCCs develop in OTRs at a significantly younger age (15 years earlier) than in the general population. This trend—which was more pronounced for kidney than heart transplant recipients—has also been observed for other epithelial malignancies, including actinic keratoses, SCC, and Merkel cell carcinoma, and could be due to the immunosuppressive treatment acting as a tumor promoter. As previously reported, we did not observe any BCC in children who had undergone transplantation; however, one of the younger OTRs with BCC (aged 29 years at the time of BCC diagnosis) had undergone several renal transplantsations during childhood, and it can be speculated that such patients may be at higher risk for BCC development because of the longer period of immunosuppression. The preponderance of BCC in men, although this hypothesis has been disputed, may play a lesser role in the development of BCC in OTRs in comparison with the general population. Risk factors specific to OTRs, such as immunosuppression and possibly human papillomavirus infection, seemingly substit
tute in these patients for the role that ultraviolet radiation plays in nonimmunosuppressed patients. In BCC in OTR, we did not observe obvious histologic signs of human papillomavirus infection (data not shown), but the demonstration of viruses within malignant tumors requires more sensitive detection techniques, such as molecular biology. However, several patients had concomitant or preceding viral warts, suggesting that HPV may have played a role in the development of BCC. Because of their possible unusual locations, BCCs may be clinically misleading in OTRs; therefore, lesions located on non–sun-exposed sites should not be overlooked but examined histologically in case of doubt. In this study, BCCs appeared on average 6.9 years after transplantation, sooner after liver than after kidney transplantation. This delay was even shorter in some studies,19 probably because of the type of organ grafted; indeed, like other skin tumors, BCCs tend to develop earlier in heart (compared with kidney) transplantation. In our study, kidney transplant recipients accounted for the majority (63.7%) of OTRs.

From a histologic point of view, we specifically studied features reflecting microscopic aggressiveness, such as histologic subtype (superficial forms being less aggressive than sclerodermiform ones, with nodular or other forms being of intermediate aggressiveness), tumor thickness, presence of ulceration, and density of the peritumoral infiltrate. In comparison with controls, BCCs in OTRs displayed some particular features. Unexpectedly, BCCs in OTRs showed overall less aggressive features than controls. Indeed, a higher percentage of them belonged to the superficial subtype, which is the least aggressive and the most amenable to simple external treatments; conversely, the proportion of sclerodermiform BCC, the most aggressive BCC subtype, was much lower in OTRs than in the control group. Referral bias may have contributed to this difference: indeed, in contrast to control patients (who seek advice spontaneously), OTRs are under close medical surveillance, and it may be argued that in this patient group more BCCs were diagnosed and excised at the early stage of superficial BCC, before progression into the invasive (nodular or sclerodermiform) stage. However, we believe it unlikely that this bias is the only cause of the differences observed between the 2 groups. The higher proportion of superficial subtypes is probably linked to the fact that a considerable percentage of tumors developed over the trunk, a preferential site for superficial BCC in the population at large.33 On the other hand, BCCs in OTRs tended to be thinner than those in controls and showed no tendency for deep tissue invasion, features most likely accounted for by the relative predominance of superficial BCC (which are thinner by definition) in the OTR group. Although BCCs in the OTRs more often showed epidermal ulceration, the difference was not statistically significant. In keeping with the lack of histologic features of aggressiveness, the course of BCCs in OTRs after treatment was uneventful. Most superficial BCCs were efficiently treated by cryotherapy (after biopsy), and the remaining ones were treated by simple surgical excision. Contrary to SCCs, which may have an aggressive course,34 in the OTRs we did not encounter BCCs with particularly aggressive behavior, in accordance with the very low BCC-related mortality rate (1%) reported in larger registries.35 Finally, in keeping with our previous findings concerning SCC,36 we found that BCCs in OTRs had a significantly reduced peritumoral inflammatory infiltrate in comparison with those in controls, a finding most likely due to the immunosuppressive treatment. Although this fact could theoretically portend a more aggressive course in skin tumors, its precise biological significance remains unclear.

In conclusion, our study shows that BCCs developing in OTRs show several differences in comparison with their “ordinary” counterparts: they appear at a younger age (especially after renal transplantation), affect predominantly men, develop more frequently on sun-protected sites (including unusual ones, such as the genitalia or axillae), and show histologically a relative predominance of the superficial subtype. These features should be known by the ever-growing number of physicians dealing with OTRs.

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REFERENCES


