On a Possible Protective Effect of HLA-A11 Against Skin Cancer and Keratotic Skin Lesions in Renal Transplant Recipients

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Renal transplant recipients who have skin cancer potentially related to human papillomavirus were HLA typed with a special focus on HLA-A11, which in nonimmunosuppressed patients is negatively associated with the occurrence of virus-related carcinoma of the cervix. We found also a negative association between HLA-A11 and skin cancer; none of the 66 transplant recipients with skin cancer were positive for HLA-A11. As HLA-A11 seems to have a protective effect against skin cancer, we speculate that antigens induced by squamous cell carcinomas and possibly also by human papillomavirus may be efficiently presented through HLA-A11 to cytotoxic T cells. We also investigated a possible influence of other HLA alleles on the susceptibility of renal transplant recipients to skin cancer. The frequency of HLA-B27 was significantly higher in the transplant recipients with skin cancer, with a relative risk of 3.4 relative to healthy controls. No significant differences were found for other HLA class I or class II antigens. J Invest Dermatol 97:269-272, 1991

Substantial evidence is accumulating that viral infections play a causative role in some human cancers [1-3]. Renal transplant recipients have a marked increase of malignancies [4] such as skin cancer [4-7], carcinoma of the cervix [8], B-cell lymphoma [4,9], and Kaposi's sarcoma [4], which are all closely linked to viral infections [9-13]. Cutaneous disorders in renal transplant recipients frequently also comprise persistent viral warts and premalignant actinic keratoses [6]. Several types of human papillomavirus (HPV) are often found in warts of renal transplant recipients [14]. Occasionally, HPV type 5 has been detected by some groups in squamous cell carcinomas [10,11], but other groups were not able to confirm this finding [15]. Furthermore, HPV-2 has been detected in a basal cell carcinoma [12] and HPV-16 in an in situ carcinoma of the penis [13] and in a squamous cell carcinoma of the vulva [14]. Strong evidence exists in nonimmunosuppressed patients of an association between carcinoma of the cervix and infection with HPV-16 and 18 [1]. An association between squamous cell carcinoma in transplant recipients and HPV-5 has been suggested [10-14], but it cannot be excluded yet that warts and skin cancer might be induced independently, by another common factor.

The major histocompatibility complex (MHC) contains a large number of polymorphic genes that encode the class I (HLA-A,B,C) and class II (HLA-DR,DQ,DP) antigens [16]. MHC antigens play an important role in host defense against viruses and against the development and spread of tumors [16,17]. HLA-associated susceptibility exists for several kinds of virus-related malignancies; Kaposi's sarcoma is associated with HLA-DR5 [18], Burkitt's lymphoma with HLA-A1,-B12, and -DR7 [19], and an association of HTLV-I infection and adult T-cell leukemia with HLA antigens has been speculated [3]. Terasaki and co-workers found a negative association of HLA-A11 with virus-related carcinoma of the cervix in nonimmunosuppressed patients [20]. The aim of this study was to confirm in renal transplant recipients the negative association of HLA-A11 with skin cancer potentially related to human papillomavirus. We also investigated a possible influence of other HLA alleles on the susceptibility of renal transplant recipients to skin cancer.

MATERIALS AND METHODS

Between March 1966 and January 1988, 764 patients received their first renal transplant at University Hospital Leiden [7]. Until October 1983 all patients received an immunosuppressive regimen consisting of azathioprine (2-2.5 mg/kg/d) in combination with low doses of prednisone (7.5-10 mg/d) [21]. From October 1983 until September 1985 all new patients were treated with either cyclosporin-A (16 mg/kg/d) or azathioprine, both in combination with low doses of prednisone [22]. From January 1986 until January 1988 all new patients received either high doses of cyclosporin-A (16 mg/kg/d) or low doses of cyclosporin-A (9 mg/kg/d) [23]. All patients were regularly seen in the out-patient nephrology clinic; those with cutaneous problems were also examined by the dermatologist.

Any suspicious lesion was biopsied and examined histologically. Only transplant recipients with histologically proved squamous cell carcinomas and basal cell carcinomas were included in the study (n = 66). As controls we used renal transplant recipients without skin cancer who had received their first renal transplant before 1981 and who were still alive with a functioning graft on July 1, 1989.
By July 1989, 66 transplant recipients had developed skin cancer. Table I shows the frequency of HLA-A3 was significantly higher in the transplant recipients with skin cancer, with a relative risk of 3.4 relative to the healthy controls (Table III). No significant differences were found for the other HLA-class I and II antigens.

When skin cancers were divided into squamous cell carcinomas and basal cell carcinomas the negative association with HLA-A11 was still significant (Table II). Basal cell carcinomas mainly accounted for the relative increase of HLA-A3 in patients with skin cancer (Table I). Squamous cell carcinoma and basal cell carcinoma contributed to the positive association between HLA-B27 and skin cancer in equal amounts (Table III).

Interestingly, HLA-A11-positive patients were only found in the group with less than 100 keratotic skin lesions (relative risk < 0.32, p = 0.097), whereas in the group with a number of keratotic skin lesions of 100 or more, again a relative increase in the number of HLA-A3 was found (relative risk 1.9, p = 0.13), although the number of patients was too small to reach statistical significance. By contrast, no association was found between HLA-B27 and the number of keratotic skin lesions.

DISCUSSION

Immunosuppressive therapy, solar radiation, and viral warts are believed to be important risk factors for the development of skin cancer in renal transplant recipients [5,6,11]. Apparently, the development of skin cancer is also influenced by the immune status of the recipient. In this study we found a protective effect of HLA-A11 against skin cancer and possibly also against keratotic skin lesions. By contrast, there was a slight relative increase in the frequency of HLA-A3, both in the patients with skin cancer and in the patients with a number of keratotic skin lesions of 100 or more. In addition, the frequency of HLA-B27 was significantly higher in the transplant recipients with skin cancer, with a relative risk of 3.4 relative to the healthy controls.

The normal cell-mediated defense against skin cancer can roughly be divided into a non-specific protection by natural killer

### Table I. Distribution of HLA-A3 in Renal Transplant Recipients with Skin Cancer and Controls

<table>
<thead>
<tr>
<th>HLA Class</th>
<th>Total skin cancer</th>
<th>SCC</th>
<th>BCC</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n = 66 (%)</td>
<td>n = 49 (%)</td>
<td>n = 32 (%)</td>
</tr>
<tr>
<td>HLA-A3</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>28 (42.4)</td>
<td>19 (38.8)</td>
<td>15 (46.9)</td>
</tr>
<tr>
<td>Negative</td>
<td>38 (57.6)</td>
<td>30 (61.2)</td>
<td>17 (53.1)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Group</th>
<th>Relative risk</th>
<th>p value</th>
<th>Corrected p value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group a</td>
<td>1.8</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Group b</td>
<td>1.3</td>
<td>0.13</td>
<td>NS</td>
</tr>
</tbody>
</table>

*NS denotes not significant; SCC, squamous cell carcinoma; BCC, basal cell carcinoma; RTR, renal transplant recipients.

### Table II. Distribution of HLA-A11 in Renal Transplant Recipients with Skin Cancer and Controls

<table>
<thead>
<tr>
<th>HLA Class</th>
<th>Total skin cancer</th>
<th>SCC</th>
<th>BCC</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n = 66 (%)</td>
<td>n = 49 (%)</td>
<td>n = 32 (%)</td>
</tr>
<tr>
<td>HLA-A11</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Negative</td>
<td>66 (100)</td>
<td>49 (100)</td>
<td>32 (100)</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Group</th>
<th>Relative risk</th>
<th>p value</th>
<th>Corrected p value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group a</td>
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<td>0.0027</td>
<td>SPS</td>
</tr>
<tr>
<td>Group b</td>
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<td>0.0069</td>
<td>SPS</td>
</tr>
</tbody>
</table>

*SPS denotes selected prospectively for study; SCC, squamous cell carcinoma; BCC, basal cell carcinoma; RTR, renal transplant recipients.

* Value corrected for 38 tested antigens.
cells and a specific HLA-restricted defense through cytotoxic T cells [26]. Furthermore, the epidermal Langerhans cells have a well-established role in the local processing and presentation of antigens to lymphocytes as a critical step in the initiation of immune responses against skin cancer [27].

Renal transplant recipients who are immunosuppressed by azathioprine and prednisone show significantly depressed NK-cell activity [28 - 30]. By contrast, T-cell-mediated immunity, as measured by responses against skin cancer [27], is essentially normal. Moreover, the epidermal Langerhans cells have a well-established role in the local processing and presentation of antigens [28].

Although cell-mediated reactions are probably of greatest significance, antibodies against tumor or viral antigens may also have important implications for host resistance. The prevalence of antibodies to human papillomavirus type 8 has reported to be significantly higher in nonimmunosuppressed patients with cervical cancer, basal cell carcinomas, and squamous cell carcinomas [32]. However, little is known of B-cell responses against human papillomavirus and skin cancer in renal transplant recipients.

HLA molecules have a key role in the generation and regulation of immune responses. The interaction of T cells with HLA antigens is essential for the subsequent activation and differentiation of T cells. Class I antigens are the targets for CD-8-positive T cells. The structure of the class I antigens is important to facilitate the recognition of viral and tumor antigens by CD-8-positive cytotoxic T cells. The amino acid sequences of HLA-A1, A3, and A11 differ only at codon 9 of the α1-domain, a critical site in the floor of the antigen-binding groove that is recognized by cytotoxic T cells [33]. In the HLA-A1 and A3 antigens, codon 9 codes for phenylalanine, and in HLA-A11 it codes for tyrosine, two amino acids that differ only in one hydroxyl group (Fig 1).

In transplant recipients, immune surveillance against skin cancer is hampered because of the depressed NK cell function. Subsequently, more strain is laid upon the functioning of the cytotoxic T cells and the role of the HLA class I antigens with respect to antigen presentation might be even more crucial. Because HLA-A11 seems to have a protective effect against skin cancer, we speculate that antigens induced by squamous cell carcinoma and possibly also by human papillomavirus may be efficiently presented by HLA-A11 to cytotoxic T cells. However, the results of in-vitro studies on the antigen-presenting capacity of HLA-A11 with regard to peptides derived from human papillomavirus and squamous cell carcinoma will have to be awaited to establish such a relationship more definitively.

**REFERENCES**


