Cell adhesion receptors in lymphoma dissemination
Drillenburg (ook Lelijveld), P.

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P. Drillenburg¹, C.M. Bronkhorst¹, A.C. van der Wal¹, L.A. Noorduyn¹, R. Hoekzema², and S.T. Pals¹

Departments of Pathology¹ and Dermatology², Academic Medical Center, University of Amsterdam, Amsterdam, The Netherlands

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Expression of adhesion molecules in pagetoid reticulosis (Woringer–Kolopp disease)

P.DRILLENBURG, C.M.BRONKHORST, A.C.VAN DER WAL, L.A.NOORDUYN, R.HOEKZEMA* AND S.T.PALS
Departments of Pathology and Dermatology, Academic Medical Centre, University of Amsterdam, 1105 AZ Amsterdam, the Netherlands
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Summary
Cell adhesion molecules play a critical role in lymphocyte migration and homing. They convey tissue-specific homing properties to lymphocyte subsets and regulate the positioning of these subsets in the body. In a patient with pagetoid reticulosis, a rare form of cutaneous T-cell lymphoma characterized by extreme epitheliotropism, we examined the expression of adhesion molecules. The neoplastic T lymphocytes showed a strong expression of cutaneous lymphocyte antigen, a skin-homing receptor which interacts with E-selectin on skin endothelium. β7, an adhesion molecule interacting with E-cadherin on epithelial cells, was also expressed on tumour cells. These findings suggest that adhesion molecules are responsible for the unique growth pattern in pagetoid reticulosis, and for the clinical behaviour of the disorder.

The formation of distinct lymphoid compartments related to specific organs, such as mucosa- or skin-associated lymphoid tissues, depends on selective recirculation and homing of lymphocytes. This homing process is carefully regulated through specialization of both endothelial cells and lymphocyte subsets in their expression and regulation of adhesion receptors and counter-receptors. By mediating interactions with the extracellular matrix (ECM) and with a variety of cells, including antigen presenting and epithelial cells, adhesion receptors also play a pivotal role in the subsequent migration and positioning of lymphocytes in the tissues.

Lymphomas are the malignant counterparts of normal lymphocytes. Adhesion receptors that direct normal lymphocyte homing (homing receptors) may hence play an important role in lymphoma dissemination. In cutaneous non-Hodgkin's lymphomas this dissemination is presumably mediated by cutaneous lymphocyte antigen (CLA), a skin homing receptor which interacts with E-selectin on skin endothelium.

Pagetoid reticulosis (PR), or Woringer–Kolopp disease, is a rare lymphoproliferative disorder which is histologically characterized by an infiltrate consisting of atypical T lymphocytes localized in the epidermis. Consistent with a neoplastic character, these T cells are monoclonal. Clinically, the disease can be subdivided into an indolent localized type and a generalized type that may run an unfavourable course. The most characteristic morphological feature is the strict cutaneous localization and the extreme epitheliotropism of the tumour cells, which suggests the involvement of a highly specific set of adhesion molecules in the pathogenesis of PR. In the present study, we have examined the expression of adhesion receptors in a patient with PR.

Case report
A 74-year-old-man was referred because of a lesion on the medial part of the left lower leg. It consisted of a flat-surfaced, scaly plaque which varied in colour (from pinkish pale to reddish brown). The diameter was 6 cm and it had a sharp irregular border (Fig. 1). Induration was minimal and the lesion was not painful. Although the colour variation of the lesion was unusual, a clinical diagnosis of Bowen's disease or superficial basal cell carcinoma was suspected and punch biopsies were taken. A biopsy taken from the affected skin was fixed in 10% buffered formalin and paraffin-embedded. A second biopsy was directly snap-frozen in liquid nitrogen. Immunohistochemical stainings were performed on frozen and/or paraffin sections using the streptavidin-biotin-peroxidase complex method (DAKO, Glostrup, Denmark). For tumour typing, a panel of commercially

Correspondence: Dr Steven T.Pals. Department of Pathology, Academic Medical Centre, University of Amsterdam, Meibergdreef 9, 1105 AZ Amsterdam, the Netherlands.
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Table 1. Expression of adhesion molecules

<table>
<thead>
<tr>
<th>Adhesion molecule</th>
<th>Positivity of tumour cells (%)</th>
<th>Intensity*</th>
</tr>
</thead>
<tbody>
<tr>
<td>α-like chain</td>
<td>0%</td>
<td>0</td>
</tr>
<tr>
<td>β-like chain</td>
<td>0%</td>
<td>0</td>
</tr>
<tr>
<td>γ-like chain</td>
<td>10%-50%</td>
<td>1+</td>
</tr>
<tr>
<td>δ-like chain</td>
<td>0%</td>
<td>0</td>
</tr>
<tr>
<td>ε-like chain</td>
<td>( \geq 90% )</td>
<td>2+</td>
</tr>
<tr>
<td>γ-like chain</td>
<td>( \geq 90% )</td>
<td>2+</td>
</tr>
<tr>
<td>δ-like chain</td>
<td>( \geq 90% )</td>
<td>2+</td>
</tr>
<tr>
<td>λ-like chain</td>
<td>( \geq 90% )</td>
<td>2+</td>
</tr>
<tr>
<td>ICAM-1</td>
<td>10%-50%</td>
<td>2+</td>
</tr>
<tr>
<td>VCAM-1</td>
<td>50%-90%</td>
<td>1+</td>
</tr>
<tr>
<td>CLA</td>
<td>( \geq 90% )</td>
<td>2+</td>
</tr>
</tbody>
</table>

* 0: no staining; 1+: moderate staining; 2+: strong staining.

available monoclonal antibodies (mAbs) against CD1, CD2, CD3, CD4, CD5, CD8, CD10, CD20, CD25, CD30, CD45, CD68, TcRaβ, TcRγδ, HLA-DR, vimentin and keratin was used (DAKO). The mAbs against adhesion molecules used were as follows: TS2/7 against α1 (CD49a) (ATCC Rockville, Maryland, U.S.A.); J143 against α2 (CD49b) (ATCC); Ber-ActS against α3 (CD103) (DAKO); 4B4 against β1 (CD29) (Coulter, Hialeah, FL, U.S.A.); BB1G11 against ICAM-1 (CD54) (British Biotechnology, Abingdon, Oxon, U.K.); 4B9 against VCAM-1 (CD106); and HECA452 against CLA. HP2/1 against α4β7 (CD49d); M17 against α6 (CD11a); and M18 against β2 (CD18) were kindly provided by Dr F. Sanchez-Madrid (Universidad Autonoma de Madrid, Spain), 1A10 against α6 (CD49f) and Act-1 against α6β7 (CD49d/β7) were a gift from Dr A. Sonnenberg (NKI, Amsterdam, the Netherlands) and Dr A.I. Lazarovits (University of Western, London, Ontario, Canada), respectively.

The skin biopsy showed an intraepithelial lesion consisting of atypical cells with a moderate amount of cytoplasm and large irregular, hyperchromatic nuclei with inconspicuous nucleoli (Fig. 2). The atypical cells were arranged as individual cells or clusters between the keratinocytes. There was no evident hyper- and/or parakeratosis. In the dermis underneath the lesion, a reactive infiltrate consisting of plasma cells and small lymphocytes was present. Immunohistochemistry on paraffin and/or frozen sections showed uniform expression of CD2, CD5, CD8, CD25, CD30, CD45, HLA-DR and TCR-αβ on the tumour cells, and hence identified them as activated cytotoxic T-lymphocytes. The tumour cells showed an adhesion phenotype as described in Table 1.

After PR was diagnosed based on the histopathological features, staging, which included a thorough physical examination, blood and bone marrow smears and a chest X-ray were performed. No evidence of internal involvement was found. The lesion was treated by radiation with 6 MeV electron beam therapy, using 20 doses of 2 Gy in 25 days. This resulted in a complete clinical remission.
Figure 3. Immunohistochemical stainings of the skin lesion: (a) cutaneous lymphocyte antigen; (b) α4β7; (c) α6β4; (d) CD30 (x175).

**Discussion**

The atypical cells in the present case of PR strongly expressed cutaneous lymphocyte antigen (CLA) (Fig. 3a). Cutaneous lymphocyte antigen is a skin-homing receptor which directs T lymphocytes to the skin through interaction with E-selectin on dermal vessels.\(^{1,9}\) In the peripheral blood, CLA is expressed on a subset of memory T lymphocytes.\(^{7-9}\) Cutaneous lymphocyte antigen expression is presumably acquired during virgin to memory transition of T cells in skin-associated peripheral lymph nodes.\(^{17}\) The CLA\(^+\) T cell population in the blood is non-overlapping with a population of gut-homing memory T cells which expresses α4β7, the receptor for the mucosal addressin MAdCAM-1.\(^{1,15}\) Consistent with this dichotomy, no expression of α4β7 was observed in the present case (Fig. 3b). Also, we observed no α4β7 expression in mycosis fungoides (unpublished observation). The expression of CLA in PR reflects its ontogenetic relation to the skin-homing T-cell subset and may contribute to the specific pattern of dissemination of the malignant lymphocytes.\(^{7-8}\)

Interestingly, all tumour cells were found to strongly express α6β4 (Fig. 3c). Under physiological conditions, α6β4 is expressed on nearly all intestinal intraepithelial lymphocytes and on approximately 50% of the T cells in the lamina propria. In the normal skin expression of α6β4 is not detected on cells in the epidermis. Cepek et al. demonstrated that α6β4 can bind E-cadherin on epithelial cells and may hence mediate positioning of lymphocytes in the epithelium.\(^{4}\) We presume that in PR, the strong α6β4 expression is a key factor in the epitheliotropism and the specific distribution of the lymphocytes between the keratinocytes (pagetoid pattern).
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LFA-1 may also contribute to this interaction since the epidermal keratinocytes in the lesions expressed ICAM-1 (not shown). In this context, the recent finding of a correlation in mycosis fungoides between loss of epitheliotropism and loss of α6ß1 expression is of interest since it also supports a role for this integrin in tumour cell interaction with the epidermis.19

To enter the epithelium, lymphocytes have to cross the epithelial basement membrane (EBM). Recently, interaction of the integrin α6ß1 to laminin-5 in the EBM, was suggested to present the first step in this process.20 In the present case, the tumour cells did not express α6. In PR the tumour cells are localized in the epithelium; down-regulation of α6 might occur after transition of the EBM.

The present tumour showed strong expression of CD30 (Fig. 3d). Among primary cutaneous T-cell lymphomas, the classical cases of mycosis fungoides/Sezary syndrome can be separated from a group of large cell lymphomas with a distinctive clinical and histological picture. Expression of CD30 on the tumour cells further subdivides this latter group since, irrespective of the morphology, expression of CD30 is related to a favourable prognosis.13 These CD30⁺ lymphomas have a tendency to remit spontaneously and are highly responsive to radiotherapy.11 CD30, a member of the TNF/NGF family, might play a direct role in causing this favourable response to therapy since triggering can induce apoptosis.21

In conclusion, this case shows that the atypical lymphocytes in PR are equipped with a set of adhesion molecules that allow specific skin-homing as well as highly effective interaction with epidermal keratinocytes. This suggests that these adhesion molecules are an important factor in determining the unique growth pattern of PR and its characteristic clinical behaviour.

Acknowledgment

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References
