Cell adhesion receptors in lymphoma dissemination

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Citation for published version (APA):
Chapter 2

Expression of the mucosal homing receptor $\alpha_4\beta_7$ in malignant lymphomatous polyposis of the intestine

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Gastroenterology 1994; 107:1519-1523
Recent studies have identified the integrin \( \alpha 4\beta 7 \) as a mucosal homing receptor that mediates lymphocyte migration to the intestinal mucosa by binding to MAdCAM-1, which is a vascular recognition molecule (adressin) selectively expressed on mucosal endothelium. The expression of the \( \alpha 4\beta 7 \) mucosal homing receptor was studied in eight cases of malignant lymphomatous polyposis (MLP). This unusual presentation of non-Hodgkin's lymphoma of mantle cell type is characterized by multifocal lymphomatous involvement of the gastrointestinal tract. Unlike nodal mantle cell lymphomas, cases of MLP showed expression of \( \alpha 4\beta 7 \), suggesting that this homing receptor plays an important role in determining the characteristic mucosal dissemination pattern of MLP.

Malignant lymphomatous polyposis (MLP) is an uncommon disease characterized by the formation of multiple lymphomatous polyps along the gastrointestinal tract. Based on its histological, cytological, and immunophenotypic characteristics, MLP is regarded as a gastrointestinal variant of the entity known as mantle cell (MC) lymphoma. The mechanisms underlying the highly characteristic clinical picture of MLP are poorly understood. However, the specific dissemination to the intestinal mucosa strongly suggests a role of tissue-specific homing mechanisms. Recent advances in the understanding of the molecular basis of mucosal lymphocyte homing now allow access to this hypothesis. In mice, high endothelial venules of Peyer's patches and lamina propria venules selectively express a glycoprotein called mucosal vascular addressin (MAdCAM-1). MAdCAM-1 is an immunoglobulin family member with domains that show homologies to the vascular adhesion receptors for leukocytes intercellular adhesion molecule 1 (CD54) and vascular cell adhesion molecule 1 (CD106) as well as to another mucosa-associated family member, immunoglobulin A1. Recent studies indicate that the integrin \( \alpha 4\beta 7 \), which is strongly expressed on mucosal lymphocytes, is the dominant lymphocyte receptor for MAdCAM-1 and for regulating lymphocyte homing to mucosal sites. In humans, \( \alpha 4\beta 7 \) seems to have a similar function. It is also expressed on mucosal lymphocytes. Moreover, it is present on a subset of peripheral blood memory T cells with putative gut homing properties.

In the present study, we have explored whether selective expression of the \( \alpha 4\beta 7 \) homing receptor might be a clue towards understanding the characteristic mucosal dissemination pattern of MLP.

### Case Reports

The major clinical findings of the eight patients with MLP are shown in Table 1. For further illustration, three cases are reported in more detail.

**Case 1**

A 67-year-old man presented with positive stool testing for blood. Colonoscopy showed several small stalked polyps scattered in the transverse and descending colon, which were endoscopically removed. Histological examination, in retrospect, showed MC lymphoma. Without further treatment, the patient presented with bloody diarrhea after a symptom-free interval of 2 years. This time, colonoscopy and barium enema (Figure 1A) showed multiple polyps throughout the entire colon, and gastroscopy showed massive thickening of the gastric folds as well as multiple duodenal polyps. Infiltration was also present in the epipharynx. Biopsy specimens documented MC lymphoma at all sites. After six terms of chemotherapy, the patient had entered a complete remission. He died at 36 months of myocardial infarction. Autopsy showed no evidence of lymphoma recidive.

**Case 2**

A 66-year-old woman presented with abdominal pain, diarrhea, and weight loss of 10 kg. At endoscopy, multiple small polyps were found in the duodenum and colon. Radiography showed peppercorn-sized polyps in the jejunum and polyps...
Table 1. Clinical Findings and Course of Disease From Eight Patients With MLP

<table>
<thead>
<tr>
<th>No.</th>
<th>Age (yr)</th>
<th>Sex</th>
<th>Presenting symptoms</th>
<th>Gastrointestinal tract site</th>
<th>Stage*</th>
<th>Therapy</th>
<th>Course (mo)</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>67</td>
<td>M</td>
<td>Bloody stools</td>
<td>Colon, stomach, duodenum,</td>
<td>III</td>
<td>CT</td>
<td>CR</td>
<td>36</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>epipharynx</td>
<td>epipharynx</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2.</td>
<td>66</td>
<td>F</td>
<td>Diarrhea</td>
<td>Colon, duodenum, jejunum</td>
<td>II</td>
<td>CT</td>
<td>PR</td>
<td>14</td>
</tr>
<tr>
<td>3.</td>
<td>78</td>
<td>F</td>
<td>Dysphagia</td>
<td>Tonsil, colon</td>
<td>N°</td>
<td>CT</td>
<td>PR</td>
<td>14</td>
</tr>
<tr>
<td>4.</td>
<td>65</td>
<td>M</td>
<td>Dysphagia</td>
<td>Stomach, duodenum</td>
<td>II</td>
<td>CT</td>
<td>Progression</td>
<td>14</td>
</tr>
<tr>
<td>5.</td>
<td>58</td>
<td>M</td>
<td>Abdominal pain</td>
<td>Stomach, colon</td>
<td>N°</td>
<td>CT</td>
<td>PR</td>
<td>2</td>
</tr>
<tr>
<td>6.</td>
<td>78</td>
<td>M</td>
<td>Weight loss</td>
<td>Colon</td>
<td>N°</td>
<td>CT/RT</td>
<td>Progression</td>
<td>38</td>
</tr>
<tr>
<td>7.</td>
<td>58</td>
<td>M</td>
<td>Dysphagia</td>
<td>Tonsil, duodenum, jejunum,</td>
<td>N°</td>
<td>CT</td>
<td>Progression</td>
<td>12</td>
</tr>
<tr>
<td>8.</td>
<td>60</td>
<td>M</td>
<td>Weight loss</td>
<td>Colon</td>
<td>N°</td>
<td>CT</td>
<td>PR</td>
<td>62</td>
</tr>
</tbody>
</table>

CR, complete remission; CT, chemotherapy; PR, partial remission; RT, radiotherapy.

*Ann Arbor system.

Case 3

A 78-year-old women presented with dysphagia caused by enlargement of the left tonsil. Biopsy specimen showed an MC lymphoma. At staging, a cervical and hilar lymphadenopathy and bone marrow involvement were found. The patient received six terms of chemotherapy at reduced dosage, resulting in a partial remission. At 14 months, routine colonoscopy showed multiple 6–8-mm polyps in a lawnlike pattern in the left-sided colon (Figure 1B). The patient refused further diagnostic procedures and therapy.

Methods

Tissue specimens of the eight patients with MLP were from the files of the Department of Pathology, University of Vienna, Vienna, Austria. They were histologically classified as MC lymphoma. Frozen tissue specimens were studied for expression of the mucosal homing receptor αβ7 by using monoclonal antibody Act-1 (immunoglobulin G1). Monoclonal antibodies against other adhesion receptors were Leu-8 (Becton Dickinson, Sunnyvale, CA) against 6-selectin; HEC-452 against CLA; TB133 against LFA-1 (CD11a); RR/1

Table 2. Expression of Adhesion Molecules in Primary Multiple MC Lymphoma of the Gastrointestinal Tract (MLP) and in Primary Nodal MC Lymphoma

<table>
<thead>
<tr>
<th>Adhesion receptor</th>
<th>Mucosal site (MLP)</th>
<th>Nodal site (MC)</th>
<th>Staining intensity</th>
<th>Staining intensity</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(no. positive/</td>
<td>(no. positive/</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>no. tested)</td>
<td>no. tested)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>α4/β7</td>
<td>8/8</td>
<td>0/5</td>
<td>1–2+</td>
<td>0</td>
</tr>
<tr>
<td>L-selectin</td>
<td>8/8</td>
<td>5/5</td>
<td>1–2+</td>
<td>1–2+</td>
</tr>
<tr>
<td>CLA</td>
<td>0/8</td>
<td>0/5</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>LFA-1 (CD11a)</td>
<td>6/8</td>
<td>3/5</td>
<td>1</td>
<td>1–2+</td>
</tr>
<tr>
<td>ICAM-1 (CD54)</td>
<td>4/8</td>
<td>2/5</td>
<td>1–2+</td>
<td>1–2+</td>
</tr>
<tr>
<td>CD44</td>
<td>8/8</td>
<td>5/5</td>
<td>2+</td>
<td>2+</td>
</tr>
</tbody>
</table>

LFA, lymphocyte function-associated antigen; ICAM, intracellular adhesion molecule.
Figure 2. MLP. (A) Dense tumor infiltration of the mucosa and submucosa of the jejunum. The surface epithelium is intact (arrows). Giemsa stain (original magnification 15x). (B) Higher magnification of A. Mucosal infiltration by mantle cells. No lymphoepithelial lesions are formed. *Lumen of a crypt (original magnification 160x). (C) Immunostaining with monoclonal antibody Act-1 directed against \( \alpha 4\beta 7 \) integrin. (D) Negative control stained with monoclonal antibody OKT-6 against CD1. (E) Positive control stained with monoclonal antibody B4 against CD19.

against intracellular adhesion molecule (CD54)\(^{12} \); HP2/1 against \( \alpha 4 \) (CD49d)\(^{13} \); and NKI-P1 against CD14.\(^{14} \) Monoclonal antibodies OKT-6 immunoglobulin G1 (Ortho Diagnostic Systems, Raritan, NY) against CD1 and B4 (immunoglobulin G1; Coulter Clone, Hialeah, FL) against CD19 were used as positive and negative controls, respectively. Immunoperoxidase staining was performed on acetone-fixed cryostat sections using the streptavidin-biotin-peroxidase complex method. Sections were counterstained with hematoxylin. Staining intensity was scored semiquantitatively on a scale of 0–2 (0, no staining; 1, weak staining; 2, moderate/strong staining). For a lymphoma to be scored positive, a minimum of 20% of the cell has to be stained.

For comparison, five cases of nodal MC lymphoma were also studied.

**Discussion**

The results of our immunohistochemical studies using monoclonal antibody Act-1 against \( \alpha 4\beta 7 \) show expression of this homing receptor in all cases of MLP examined (Table 2 and Figure 2A–C). In each case, expression of \( \alpha 4\beta 7 \) was detectable on a majority of the tumor cells. The expression level on individual tumor cells was heterogeneous and ranged from moderate to weak. By contrast, \( \alpha 4\beta 7 \) was absent from nodal MC.
lymphomas (Table 2). This difference between MC lymphoma of the gastrointestinal tract (i.e., MLP) and nodal MC lymphoma did not reflect a general difference in the regulation of adhesion molecule expression but was specific for αβ7 (Table 2). Expression of a number of other adhesion receptors involved in lymphocyte-endothelial cell interaction and lymphocyte homing, including T-selectin, cutaneous lymphocyte antigen, leukocyte function–associated antigen 1 (LFA-1α, CD11a), intercellular adhesion molecule 1 (ICAM-1, CD54), VLA-4 (CD49d), and CD44 in nodal MC and MLP, was not different (Table 2). Hence, αβ7 is specifically expressed in MLP and might mediate the mucosa-specific tumor dissemination that is characteristic of this disease.

Maintenance of the integrity of distinct lymphoid compartments, such as mucosa-associated lymphoid tissues, is critically dependent on selective recirculation and homing of lymphocytes. Results from a large body of studies show that this homing process is carefully regulated through specialization of both endothelial cells and lymphocyte subsets in both their expression and regulation of adhesion receptors and counterreceptors. αβ7 in non-Hodgkin’s lymphomas, the normal expression programs of these receptors seem to be at least partly preserved. Like in normal lymphocytes, adhesion receptor expression in lymphomas is related to their stage of maturation and anatomic localization. This selective receptor expression seems to contribute importantly to the specific patterns of dissemination of non-Hodgkin’s lymphomas. This notion is not only supported by the selective expression of αβ7 in MLP as found in our present study. Previous studies from our own and other laboratories have shown that the skin homing receptor cutaneous lymphocyte antigen is selectively expressed on cutaneous T-cell lymphomas. Furthermore, expression of αβ7 mucosal homing receptor is not unique to MLP, but this molecule is also expressed on other lymphomas of mucosa-associated lymphoid tissue (unpublished observation). The close relationship between the expression of particular tissue-specific homing receptors and the anatomic site of lymphoma involvement suggests that lymphomas at different sites may represent biologically distinctive groups of tumors, a notion that is also emerging from recent clinical, morphological, and molecular genetic studies. Assessment of homing receptor expression in non-Hodgkin’s lymphomas, which can be performed by routine immunohistochemistry, may contribute to the classification of non-Hodgkin’s lymphomas and may help to predict lymphoma dissemination.

References

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Received February 3, 1994. Accepted July 4, 1994.
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Supported by grant IKA-91/9 of the Dutch Cancer Foundation and the Crohn's and Colitis Foundation of Canada.

The authors thank Drs. R. A. W. van Lier, E. G. Butcher, T. A. Springer, F. Sanchez-Madrid, and C. G. Figdor for providing monoclonal antibodies, and M. Burghuber and I. Mosberger for technical assistance.