Somatostatin Receptor Expression in Primary Gastric Versus Nongastric Extranodal B-Cell Lymphoma of Mucosa-Associated Lymphoid Tissue Type

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Lymphoma of the mucosa-associated lymphoid tissue (MALT) type represents a distinct clinicopathologic entity (1,2). The majority of these lymphomas occur in the stomach, but they may also be found in the thyroid and salivary glands, lung, breast, and ocular adnexa where they tend to remain localized for a prolonged period of time (3). Before therapy is initiated for these lymphomas, there is widespread consensus about the importance of thorough staging, including otorlaryngologic investigation, computerized tomography of the abdomen and thorax, gastroscopy, endosonography, colonoscopy, as well as enteroclysis and bone marrow biopsy (4), since stage influences prognosis and choice of therapeutic strategies (5,6). Although endosonography is highly sensitive for focal penetration and evaluation of regional lymph nodes (7), additional methods for imaging might still be needed to facilitate clinical decision making. Because of the finding that malignant lymphomas express somatostatin receptors (SSTRs), pilot studies have been performed using somatostatin analogues as therapeutic agents (8), and radiolabeled octreotide (OCT), a long-acting somatostatin analogue preferentially binding to SSTR subtypes 2 and 5, has been used for imaging of such tumors (9–11), allowing for estimation of the tumor burden after a single tracer injection.

We have performed a study to investigate the potential of commercially available $^{111}$In-DTPA-D-Phe$^1$-OCT (OctreoScan®, Mallinckrodt Medical, Northampton, U.K.; referred to hereafter as $^{111}$In-OCT) for staging of patients with MALT-type lymphoma along with in vitro evaluations of SSTR expression in human samples of both gastric and extragastric origins.

Histologic diagnosis of low-grade lymphoma of the MALT type was performed according to the criteria outlined by Isaacson and co-workers (1,2). In addition, immunologic phenotyping on paraffin sections demonstrated light chain restriction in all cases, indicating monoclonal B-cell proliferation, and revealed the phenotype CD20$^+$CD5$^-$CD10$^-$, which, in context with the microscopic appearance, is consistent with low-grade B-cell lymphoma of the MALT type (2). The diagnosis of high-grade lymphoma was based on the presence of large cells with a blastic appearance growing in sheets (often between glands), with or without a low-grade component, and was also confirmed by phenotyping. In patients with a predominance of a large-cell component, the presence of a low-grade component defined the MALT origin of the lymphoma, and also pure large-cell lymphomas without evidence of extragastric spread were included.

All patients underwent otorlaryngologic investigation, gastroscopy with multiple biopsies, enteroclysis, colonoscopy, bone marrow biopsy, endosonography, and computed tomography scans of the thorax and abdomen. Staging was performed according to the criteria of Rohatiner et al. (4).

Included in this study were 29 consecutive patients (16 females and 13 males) aged 32–88 years with histologically verified lymphoma of the MALT type in clinical stage I (16 patients) and stage II (13 patients). Eighteen patients presented with primary gastric MALT-type lymphoma: Seven patients had gastric low-grade lymphoma, two had high-grade lymphoma with a low-grade component, and nine had a lymphoma of high-grade histology. Two patients with a lymphoma of high-grade histology had undergone gastrectomy for acute perforation but had lymph nodes involved in situ, while one additional patient presented with pulmonary relapse 6 years after gastrectomy because of a low-grade MALT-type lymphoma. Ten patients had primary extragastric manifestations of low-grade histology: Two had lymphoma of the conjunctiva, three had lymphoma of the lung, two had parotid lymphoma, and one patient each had lymphoma of the breast and the lacrimal gland. One patient with a history of Sjögren’s syndrome and involvement by low-grade MALT-type lymphoma underwent cervical lymphadenectomy for diagnosis.

For imaging purposes, the commercially available OctreoScan® was used according to the manufacturer’s description, and gamma camera imaging consisting of both planar imaging and single-photon emission tomography was performed according to published standard methods (12).

Informed consent according to institutional guidelines was obtained from all patients. The Ethical Board of the University of Vienna approved of the application of the tracer to humans.

We examined six tumor samples obtained at surgery for expression of messenger RNA (mRNA) of SSTR subtypes (SSTR1–SSTR5) by means of northern blotting according to previously published methods (13). We also investigated two cases of low-grade MALT-type lymphoma of extragastric origin (i.e., one pulmonary lymphoma and one cervical lymph node) from patients undergoing $^{111}$In-OCT scintigraphy. In addition, we evaluated four gastrectomy specimens (one low-grade lymphoma, one high-grade lymphoma with a low-grade component, and two high-grade lymphomas) including those of two patients imaged with $^{111}$In-OCT. Twenty-eight patients were considered evaluable, while one patient was excluded from the analysis because additional chronic lymphocytic leukemia was present. In patients with gastric MALT-type lymphoma, results were disappoint-
manifestations, In-OCT scintigraphy of the 10 patients with primary extragastric lymphomas showed no lymph node accumulation. In addition, no lymph node involvement was imaged in patients with documented stage II disease. In all the 10 patients with primary extragastric manifestations, 111In-OCT scintigraphy resulted in the visualization of the neoplastic lesions present. Two patients underwent a second injection of the tracer after successful local irradiation, and no focal tracer uptake could be demonstrated. In one patient who presented with pulmonary relapse after resection of a primary low-grade MALT-type lymphoma of the stomach, however, no tracer uptake in the pulmonary lesions could be demonstrated.

A different pattern of SSTR-subtype expression between gastric and extragastric MALT-type lymphomas was detected by northern blotting. Extragastric lymphomas expressed large amounts of mRNA for SSTR2, while gastric samples showed expression of mRNA for SSTR3 and also for SSTR4 but not for SSTR2 (Table 1). Our findings with regard to the mRNA level suggest a molecular difference between gastric and extragastric MALT-type lymphomas. While caution appears necessary because of the small sample size in both groups, these results are further supported by our scanning data: Primary extragastric MALT-type lymphomas could be readily visualized by 111In-OCT scanning in all patients (Fig. 1, upper panels), which reflects the high level of expression of SSTR2 as seen in our samples in vitro. Especially noteworthy is the fact that one patient who presented with pulmonary relapse after initial resection of a gastric lymphoma showed no tracer uptake within the lung lesions. Thus, extragastric MALT-type lymphomas could be potential candidates for inclusion of 111In-OCT scanning into the diagnostic armamentarium and probably also for treatment with somatostatin analogues targeting SSTR2, since this receptor has been implicated in the growth control of malignant cells (14). In contrast, gastric samples did not express sufficient amounts of SSTR2 and, therefore, could not be imaged by

Table 1. Northern blot analysis of relative messenger RNA expression of somatostatin receptor (SSTR) subtypes 1–5 as judged by laser densitometry

<table>
<thead>
<tr>
<th>Tumor samples†</th>
<th>SSTR1</th>
<th>SSTR2</th>
<th>SSTR3</th>
<th>SSTR4</th>
<th>SSTR5</th>
</tr>
</thead>
<tbody>
<tr>
<td>COS7 cells (control)</td>
<td>0.06 (0.03)</td>
<td>0.10 (0.03)</td>
<td>0.16 (0.09)</td>
<td>0.03 (0.02)</td>
<td>0.12 (0.07)</td>
</tr>
<tr>
<td>Lung/LG</td>
<td>0.00 (0.00)</td>
<td>1.03 (0.11)</td>
<td>0.32 (0.09)</td>
<td>0.13 (0.08)</td>
<td>0.07 (0.02)</td>
</tr>
<tr>
<td>Lymph node/LG</td>
<td>0.00 (0.00)</td>
<td>0.96 (0.12)</td>
<td>0.27 (0.09)</td>
<td>0.08 (0.03)</td>
<td>0.12 (0.04)</td>
</tr>
<tr>
<td>Gastric</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LG</td>
<td>0.00 (0.00)</td>
<td>0.03 (0.02)</td>
<td>0.17 (0.02)</td>
<td>0.66 (0.13)</td>
<td>0.04 (0.03)</td>
</tr>
<tr>
<td>LG + HG</td>
<td>0.00 (0.00)</td>
<td>0.17 (0.05)</td>
<td>0.25 (0.06)</td>
<td>0.28 (0.04)</td>
<td>0.10 (0.06)</td>
</tr>
<tr>
<td>HG</td>
<td>0.00 (0.00)</td>
<td>0.00 (0.00)</td>
<td>0.17 (0.03)</td>
<td>0.21 (0.01)</td>
<td>0.07 (0.02)</td>
</tr>
<tr>
<td>HG</td>
<td>0.00 (0.00)</td>
<td>0.04 (0.01)</td>
<td>0.83 (0.11)</td>
<td>0.60 (0.04)</td>
<td>0.11 (0.08)</td>
</tr>
</tbody>
</table>

†LG = low grade; HG = high grade.

*Results of laser-densitometric measurements obtained with northern blot analysis with higher numeric values corresponding to higher signal intensity on x-ray films. Laser-densitometric measurements were performed by use of the GelScan XL® software (Pharmacia, Uppsala, Sweden) with an automatic correction for background. COS7 cells (a simian virus 40-transformed monkey kidney fibroblast-like cell line) with a documented absence of all SSTR subtypes were used as negative controls. For gel electrophoresis, 20 μg of RNA of each tumor sample was used for hybridization for each SSTR-specific probe. Blots were done in triplicate. Values in columns are given as means (standard deviation) to allow for comparison of relative messenger RNA expression.
means of $^{111}$In-OCT scanning (Fig. 1, lower panels). However, our findings suggest that $^{111}$In-OCT is a potential tool for discriminating between gastric and extragastric origins of the MALT-type lymphoma. Further investigations on gastric MALT-type lymphoma are needed to evaluate the function and density of SSTR3 and SSTR4 in this disease, as well as the potential application of somatostatin analogues targeting these SSTR subtypes for diagnosis and treatment.

REFERENCES


NOTE

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