Monoclonal Immunoglobulin Production Is a Frequent Event in Patients with Mucosa-Associated Lymphoid Tissue Lymphoma

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ABSTRACT
Purpose: Mucosa-associated lymphoid tissue (MALT) lymphoma comprises 7% of all newly diagnosed non-Hodgkin's lymphomas and is therefore among the most common lymphoma entities. Monoclonal gammopathy due to production of a monoclonal immunoglobulin by lymphoma cells is a well-known phenomenon associated with various types of B-cell non-Hodgkin's lymphomas. The objective of the present study was to evaluate the incidence and clinical relevance of paraprotein (PP) production in patients with MALT lymphoma.

Experimental Design: Fifty two patients were prospectively evaluated with regard to differentiation of the MALT lymphoma cells, t(11;18) translocation, monoclonal immunoglobulin production, Helicobacter pylori (HP) status, stage, treatment, and clinical outcome.

Results: Nineteen of 52 MALT lymphoma patients (36%) had PP (8 IgMκ, 6 IgGκ, 4 IgMλ, and 1 IgAκ). The histologic feature of plasmacytic differentiation correlated significantly with the production of PP (P = 0.001). No correlation was found between PP and clinical stage, HP status, and t(11;18) status. PP was, however, negatively associated with response to eradication of HP in gastric MALT lymphoma, and PP levels declined significantly in patients responding to chemotherapy or radiation. Importantly, both immunofixation and serum electrophoresis have to be performed to detect low PP levels.

Conclusions: In conclusion, PP levels may probably be used as a potential prognostic tool for response to HP eradication, and serial measurements may also allow for noninvasive assessment of response to radiation or chemotherapy in patients with MALT lymphoma.

INTRODUCTION
Production of a monoclonal immunoglobulin/paraprotein (PP) by lymphoma cells is a well-known phenomenon associated with various types of B-cell non-Hodgkin's lymphomas (NHLs; ref. 1). Extranodal marginal zone (MZ) B-cell lymphoma of mucosa-associated lymphoid tissue (MALT) is a distinct clinicopathological entity initially defined by Isaacson and Wright in 1983 (2), which has been incorporated into the recent World Health Organization classification of hematologic malignancies (3). MALT lymphoma comprises 7% of all newly diagnosed NHLs and is therefore among the most common lymphoma entities (3).

The postulated cell of origin of MALT lymphoma is the MZ B cell corresponding to a post germinal center B cell with rearranged and mutated immunoglobulin heavy and light chain genes (3). MZ cells are thought to capture, process, and present antigens and deliver costimulatory signals to T cells. In addition, they apparently display the capacity to differentiate into plasma cells, and most early antibody-secreting cells are thought to originate from MZ B-cell precursors (4). In keeping with this hypothesis, MALT lymphomas often include high numbers of plasma cells, a phenomenon termed plasmacytic differentiation (3). This feature is especially prominent in a special, albeit rare, type of MALT lymphoma termed immunoproliferative small intestinal disease (5, 6), but it may also explain cases initially described as extramedullary plasmacytoma within classical MALT organs such as the gastrointestinal tract, which might in fact be MALT lymphomas with extreme plasmacytic differentiation.

The close relationship of MZ B cells with plasma cells suggests a potential for immunoglobulin production by MALT lymphoma cells, which has been reported by various authors, albeit in anecdotal form (7–10). To date, however, no systematic investigations to assess the frequency of monoclonal immunoglobulin/PP production have been performed in patients with MALT lymphoma. Therefore, the objective of the present analysis was to study the incidence and clinical relevance of PP in MALT lymphoma patients diagnosed and treated at our institution.

PATIENTS AND METHODS
All patients with histologically verified, previously untreated MALT lymphoma admitted at our institution since the beginning of 2001 were prospectively evaluated.

Histopathological diagnosis was established according to the criteria defined by Isaacson and Wright (2), initially adopted in the revised European American lymphoma and later adopted in the recent World Health Organization classification for MALT lymphoma (11). In all patients, immunologic phenotyping on paraffin sections was done for demonstration of heavy and light chain restriction and for the phenotype CD20+/CD5−CD10−cyclinD1+, which, in context with the microscopic appearance, is consistent with MALT lymphoma. Plasmacytic differentiation was defined.
as the presence of sheets of light chain-restricted plasma cells. All samples were evaluated by a single reference hematopathologist (A. C.) to avoid a potential bias caused by interobserver variability. In addition, reverse transcription-polymerase chain reaction on paraffin-embedded biopsy sections for assessment of the t(11;18) translocation was performed.

Clinical information evaluated included the following: localization of the lymphoma, clinical stage, both serum electrophoresis (Olympus Hite 630; Goffin Meyvis, Etten-Leur, the Netherlands) and serum immunofixation (Hydragel 9 IF; Sebia, Norcross, GA) according to standard methods in all patients, quantitative levels of serum immunoglobulins (IgG, IgM, and IgA), the presence of an underlying autoimmune disease, *Helicobacter pylori* (HP) status, treatment, response to therapy, follow-up time, and survival.

**RESULTS**

Fifty two consecutive patients with previously untreated MALT lymphoma (31 patients with extragastric lymphoma and 21 patients with gastric lymphoma) were evaluable for analysis (see Table 1), and PP production was found in 19 of 52 patients (36%).

Eight of these 19 patients (42%) had IgM, 6 of 19 patients (31%) had IgG, 4 of 19 patients (21%) had IgMA, and 1 of 19 patients (5%) had IgAc. The serum PP corresponded with the light chains detected on biopsy specimens in all patients, and a 79% correspondence with the immunohistochemical results for heavy chains was found. Two of the patients with discordance between serum PP and the heavy chains on biopsy specimens had IgGc, one had IgMx, and one had IgAc. Interestingly, 4 of the 19 patients (21%) with PP had a positive immunofixation but a normal serum electrophoresis pattern. The levels of uninvolved immunoglobulin were depressed in 5 of 19 (26%) patients with serum PP (IgG and IgM in two patients each and IgA in one patient).

Twelve of 31 patients (39%) with extragastric MALT lymphoma and 7 of 21 patients (33%) with gastric lymphoma had PP. The presence of PP was not indicative of clinical stage: 12 of 19 patients (63%) had stage I or II disease, and 7 of 19 patients (37%) had stage IV disease. Only 1 of 11 patients with an underlying autoimmune disease, *i.e.*, Sjögren’s syndrome, also had evidence of PP. Among the 21 patients with gastric MALT lymphoma, 15 (71%) had signs of HP infection. Overall, no correlation between PP and HP status was found because 5 of 7 patients (71%) with PP and 10 of 14 patients (71%) without PP were HP positive.

None of the seven gastric MALT lymphoma patients with PP responded to eradication of HP, whereas four PP-negative patients showed remission of the lymphoma after antibiotic treatment. Three of the 7 nonresponders were positive for t(11;18). The t(11:18) translocation did not correlate with the presence of PP. In addition, none of these seven cases had evidence of an underlying autoimmune disease.

As expected, plasmacytic differentiation correlated significantly (*P* = 0.001) with the presence of PP because 10 of 19 patients (53%) with detectable PP were found to have plasmacytic differentiation as opposed to 3 of 33 patients (9%) without PP. In total, 13 of 52 patients (25%) had plasmacytic differentiation, including 3 of 21 patients (14%) with gastric lymphoma and 10 of 31 patients (32%) with extragastric lymphoma. Interestingly, plasmacytic differentiation was present in only 1 of 11 patients with Sjögren’s syndrome, but this patient had no evidence of PP production.

Overall, good correlation was noted between PP and therapeutic response in patients undergoing serial evaluation of PP levels. A decrease of PP corresponded to a clinical response, and the median level decreased significantly (*P* = 0.003) from 21.4 g/liter (range, 9.5–47.9 g/liter) before treatment to 14.2 g/liter (range, 8.7–39.5 g/liter) after treatment, but it did not reach normal levels in the patients for whom quantitative assessment was possible (see Table 2). One patient who had a normal serum electrophoresis but showed an indication of PP on immunofixation became PP negative after successful treatment resulting in complete remission as judged by conventional staging.

**DISCUSSION**

Production of a serum PP has been reported repeatedly in patients with various forms of NHL (1, 12–14) but has been judged to be a rare event in patients with MALT lymphoma (15). However, no systematic investigations on this topic are available in the recent literature, which has prompted us to prospectively study all patients with untreated MALT lymphoma admitted at our institution as of the beginning of 2001. Our analysis disclosed a detectable serum PP in 19 of 52

### Table 1  Patient characteristics

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Patient characteristics</th>
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<tbody>
<tr>
<td>No. of patients</td>
<td>52</td>
</tr>
<tr>
<td>Median age (yrs) (range)</td>
<td>57 (22–85)</td>
</tr>
<tr>
<td>No. of patients with t(11;18)</td>
<td>13</td>
</tr>
<tr>
<td>No. of patients with HP infection</td>
<td>30</td>
</tr>
<tr>
<td>No. of patients with PP</td>
<td>19</td>
</tr>
<tr>
<td>Median survival (mo)</td>
<td>+204 (not reached)</td>
</tr>
<tr>
<td>No. of patients with stage I disease</td>
<td>29</td>
</tr>
<tr>
<td>No. of patients with stage II disease</td>
<td>11</td>
</tr>
<tr>
<td>No. of patients with stage III disease</td>
<td>1</td>
</tr>
<tr>
<td>No. of patients with stage IV disease</td>
<td>11</td>
</tr>
<tr>
<td>No. of patients with plasmacytic differentiation</td>
<td>13</td>
</tr>
</tbody>
</table>

Abbreviation: Pat. ev., evaluable patients.

**Table 2  Changes in median serum PP during therapy**

<table>
<thead>
<tr>
<th>PP before therapy</th>
<th>PP after therapy</th>
<th>Difference</th>
</tr>
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<tbody>
<tr>
<td>IgG</td>
<td>21.1 (11.9–36.5)</td>
<td>14.9 (10.8–18.6)</td>
</tr>
<tr>
<td>IgM</td>
<td>28.7 (9.5–47.9)</td>
<td>13.2 (8.7–39.5)</td>
</tr>
<tr>
<td>Σ</td>
<td>21.4 (9.5–47.9)</td>
<td>14.4 (8.7–39.5)</td>
</tr>
</tbody>
</table>

**NOTE.** Values represent serum PP in g/liter; range is shown in parentheses. Abbreviation: Σ, IgG + IgM.
patients (36%) evaluated by both serum electrophoresis and immunofixation, which is one of the highest frequencies of PP production in lymphoma documented to date. As opposed to this, lower frequencies have been published for various other types of NHL (1, 12–14), and a recent report has documented the occurrence of PP in 20.2% of patients with indolent types of NHL (12), whereas it appears to be rare in aggressive lymphomas. In our cohort, the serum PP corresponded with the light chains detected on biopsy specimens in all patients, and a 79% correspondence with the immunohistochemical results for heavy chains was found. According to this striking correspondence, the most likely explanation for PP in our patients is the production of the immunoglobulins by the clonal lymphoplasmocytic cells. In four patients, however, a discordance between serum PP and heavy chains was found, suggesting a possible coincidence of MALT lymphoma and monoclonal gammopathy of undetermined significance. Because a likelihood of 3% for monoclonal gammopathy of undetermined significance (15) has been reported in elderly patients, such an association appears to be possible, especially in patients with IgGκ (which was indeed present in two of four cases). The fact that all patients were negative for the MALT lymphoma-specific t(11;18) further supports this notion.

Of interest is the fact that 4 of 19 patients (21%) had evidence of PP on immunofixation, whereas the conventional serum electrophoresis pattern was not indicative of PP. Thus, the amount of circulating PP was apparently below the detection threshold of standard serum electrophoresis, and PP production would have been missed without performance of additional immunofixation. According to this finding, one may hypothesize that PP production may have been underestimated thus far in patients with MALT lymphoma in the absence of routine performance of immunofixation.

A significant correlation of PP with plasmacytic differentiation (P = 0.001) was found, which was present in 13 of 52 patients (25%). This percentage is in keeping with data in the literature estimating plasmacytic differentiation in up to 30% of MALT lymphomas (15). Plasmacytic differentiation, however, was more prominent in patients with extragastic origin of MALT lymphoma (32% versus 14% in gastric lymphoma) but was present in only 1 of 11 patients with an autoimmune disease.

PP production was not correlated with clinical stage, HP status, or the presence of t(11;18) in our patients. This is especially noteworthy because none of the seven gastric MALT lymphoma patients with PP responded to eradication of HP, whereas four PP-negative patients showed remission of the lymphoma after antibiotic treatment. Only three of the seven nonresponders were found to be positive for t(11;18), a factor that has consistently been shown to be associated with a lower response rate of gastric lymphoma to HP eradication. In addition, none of these patients suffered from an underlying autoimmune disease, which has also been shown as a negative prognostic factor for response to eradication of HP. Whereas the small number of patients does not allow for statistically significant comparison, these data nevertheless suggest the presence of PP as a potential additional prognostic factor for response to HP eradication.

Overall, a good correlation between clinical response and PP levels could be demonstrated. A decrease of PP corresponded to a clinical response, and the median level decreased significantly (P = 0.003) from 21.4 g/liter (range, 9.5–47.9 g/liter) before treatment to 14.2 g/liter (range, 8.7–39.5 g/liter) after treatment (see Table 2), and one patient with PP detectable only on immunofixation became negative after successful treatment resulting in complete remission.

In conclusion, our data suggest that monoclonal gammopathy is a common phenomenon in patients with MALT lymphoma, most probably due to PP production by the clonal lymphoplasmacytic cells. However, it is important to perform both immunofixation and conventional serum electrophoresis to detect even low levels of monoclonal immunoglobulins. PP levels may not only be used as a potential prognostic tool for response to HP eradication, but serial measurements may also allow for noninvasive assessment of response to radiation or chemotherapy.

REFERENCES

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