An Immunohistochemical Analysis of Gastric B-cell Lymphomas: Stromal Cells Exhibit Peculiar Histogenesis in Gastric B-cell Lymphomas

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Anti-Helicobacter pylori (HP) therapy succeeded in regressing gastric B-cell lymphomas (gBL) with a close relation to infestation of HP, although the exact mechanism of anti-HP therapy in gBL has not yet been clarified. In order to see a part of the mechanism, this study analyzed stromal cells in 34 gBL cases comprised of 11 cases of mucosa-associated lymphoid tissue (MALT) type and 24 cases of diffuse large B-cell lymphoma (DLBL) by means of immunohistochemistry of CD3, CD5, CD79a, CD68, CD21, S100 protein, thymidine phosphorylase (TP) and inducible nitric oxide synthase (iNOS). Numerous CD68-positive stromal cells were seen in 9 cases of MALT type and 22 cases of DLBL. Many dendritic cells (DC) expressed TP and formed an ill-defined meshwork in the background in 8 cases of MALT type and 17 cases of DLBL. In most cases, transition of CD68-positive stromal cells to DC expressing TP was recognized. There was more or less intermingling of CD3-positive T-cells in all cases. Expression of iNOS was seen in some stromal cells and glandular epithelial cells, but only in 3 cases of MALT type. In the germinal center (GC) colonization of MALT type there were CD21-positive follicular DC, CD68-positive stromal cells, TP-expressing DC and iNOS-expressing cells; whereas in that of DLBL the meshwork of CD21-positive follicular DC was destroyed and the stromal cells did not express TP or iNOS. Then, a peculiar co-existence of intermingling T-cells, CD68-positive stromal cells, DC expressing TP forming an ill-defined meshwork, and lymphoma cells were recognized in gBL. A small number of stromal cells and glandular epithelial cells expressed iNOS and prepared a nitric oxide-rich microenvironment for growth and transformation of MALT type lymphoma cells. This peculiar histogenesis of gBL was thought to explain a part of the mechanism of the anti-HP therapy against gBL.

Key words: gastric B-cell lymphoma, T-cell-associated dendritic cells, thymidine phosphorylase, CD68, inducible nitric oxide synthase (iNOS)

I. Introduction

Most gastric B-cell lymphomas (gBL) are believed to be Helicobacter pylori (HP)-related cases of mucosa-associated lymphoid tissue (MALT) type [25, 59] of marginal zone B-cell lymphoma (MzBL) or diffuse large B-cell lymphoma (DLBL). But a direct relation between HP infection and the occurrence of gBLs has not yet been clarified.

Anti-HP therapy succeeded in regressing gBL, even in some cases of DLBL [1, 8, 11, 40, 41, 47], suggesting that the growth of gBL cells depends on unknown mechanisms that anti-HP therapy can suppress. This study analyzed immunological phenotypes of stromal cells in gBL and found an increase of dendritic cells (DC) that were positive for...
CD68 and expressed thymidine phosphorylase (TP) [16] in many cases. Because synovial cells can express TP under T-cell stimulation [42, 57], anti-HP T-cell immunity [4, 12, 32, 45, 50, 56] may induce many T-cell-associated DC expressing TP in the background of gBL. On the other hand, we speculated that lipopolysaccharides (LPS) of HP bodies, Lewis X and Y, indirectly induced a nitric oxide (NO)-rich microenvironment in germinal centers (GC) in the regional lymph nodes [17] of the stomach with HP-related peptic ulcers [20]. The NO may disturb anti-HP B-cell immunity and evoke oncogenic changes in post-GC B-cells as candidate cells of MALT type gBL. Then, expression of inducible nitric oxide synthase (iNOS) in gBL was also examined. The expression of iNOS was seen in GC with lymphoma cell colonization and in glandular cells of the mucosa in MALT type gBL. Therefore, we thought that the unknown mechanism may be a dependence of gBL cells on the increased T-cell-associated DC expressing TP. The NO-rich microenvironment in the GC and in the mucosa probably encouraged proliferation of MALT type gBL cells and possibly played a role in the transformation of MALT type lymphoma cells to large lymphoma cells.

Below is an immunohistochemical analysis of stromal cells in gBL and a discussion of the histogenesis of gBL and its relation to the mechanism of anti-HP therapy against gBL.

II. Materials and Methods

Thirty-four cases of gBL were diagnosed in the Department of Pathology, the first University Hospital, China Medical University and its related laboratories. Representative paraffin sections of these gBL cases were selected in the Department of Pathology, China Medical University. Without any information about the patients, these paraffin sections were analyzed in the Departments of Pathology and Anatomy, Kagoshima University Faculty of Medicine.

Table 1. Antibodies employed in this study

<table>
<thead>
<tr>
<th>Antibody</th>
<th>Source</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>anti-CD3</td>
<td>NCL-CD3-PS1, Novo^41, monoclonal</td>
<td>Pan-T cells</td>
</tr>
<tr>
<td>anti-CD5</td>
<td>NCL-CD5-IC7, Novo^41, monoclonal</td>
<td>T cells and pre-GC B cells</td>
</tr>
<tr>
<td>anti-CD79a</td>
<td>M7050, DAKO^62, monoclonal</td>
<td>Pan-B cells</td>
</tr>
<tr>
<td>anti-CD68</td>
<td>M0876 (=PGM1), DAKO^2, monoclonal</td>
<td>Macrophages and dendritic cells</td>
</tr>
<tr>
<td>anti-CD21</td>
<td>NCL-CD21, Novo^41, monoclonal</td>
<td>Follicular dendritic cells</td>
</tr>
<tr>
<td>anti-S100 protein</td>
<td>DAKO S100, DAKO^2, polyclonal</td>
<td>Interdigitating dendritic cells</td>
</tr>
<tr>
<td>anti-TP</td>
<td>Supplied from Akiyama S, monoclonal</td>
<td>Thymidine phosphorylase (TP)</td>
</tr>
<tr>
<td>anti-iNOS</td>
<td>No. 4827/28, Calbiochem^42, polyclonal</td>
<td>iNOS^44</td>
</tr>
</tbody>
</table>

#1: Novo Castra, Newcastle, UK.
#2: Dako A/S Glostrup, Denmark.
#3: Calbiochem, a brand of CN Biosciences, Inc, an Affiliate of Merck KGaA, Darmstadt, Germany.
#4: Inducible nitric oxide synthase (iNOS).

Immunohistochemistry of lymphoma cells and stromal cells

After deparaffination and inactivation of endogenous peroxidase by incubation in 3% hydrogen peroxide (H2O2) methanol solution for 20 min, the sections were processed with antigen retrieval that consisted of incubating sections in 0.01 M citrate buffer pH 6.0, heating them by means of an autoclave for 5 min at 121°C, and cooling them in phosphate buffered saline (PBS).

The sections were reacted with the primary antibodies listed in Table 1. Reacted primary antibodies were made visible by means of avidin-biotin complex (ABC) method and H2O2-diaminobenzidine (DAB) reaction. After nuclear counterstain by hematoxylin, sections were dehydrated and mounted in plastic medium.

Evaluation of immunological phenotype of lymphoma cells and stromal cells

CD79a-positive and CD5-positive or negative lymphoma cells were evaluated as those of B-cell type. Lymphoma cells of pre-germinal center B-cells were positive for CD79a and CD5. MALT type MzBL cells were positive for CD79a and negative for CD5. T-cell lymphoma cells were positive for CD3 and CD5. Based on the histology and immunological phenotype, the gastric lymphomas were categorized according to the new WHO classification [26].

As for S100 protein-positive stromal cells, based on the previous studies [14, 15], the increase of S100 protein-positive cells was evaluated. As for CD68-positive stromal cells, it was evaluated as having increased according to the distribution pattern of S100 protein-positive stromal cells [15].

As for CD21-positive cells, it was evaluated as having increased when sporadic aggregation of CD21-positive cells was seen as in angioimmunoblastic T-cell lymphoma [27].

TP is labeled in the nucleus, when cells maintain active thymidine metabolism. Because DC in the background of mature T-cell neoplasms were labeled by anti-TP antibody and formed a meshwork [16], the increase of TP-positive cells with a tendency to form a meshwork of dendritic cytoplasm was evaluated as an increase of TP-positive cells.

The specificity of each antibody-labeled cell is listed in Table 1.

III. Results

Based on the histology and immunological phenotype examined, the 34 cases of gBL comprised 11 cases of MALT type MzBL and 23 cases of DLBL according to the new WHO classification [26]. In these gBL cases there was more or less CD3-positive intermingling T-cells among lymphoma cells.

In the case of MALT type (Fig. 1), lymphoma cells...
Fig. 1. A case of MALT type MzBL. a) Hematoxylin-Eosin stain (H.E.). b) CD79a. c) CD68. d) Anti-TP. e) Anti-S100 protein. f) Anti-iNOS. Small to medium-sized centrocyte-like cells proliferated in the deep areas of the mucosa (a). The lymphoma cells were positive for CD79a (b) and negative for CD3 and CD5. Some intermingling stromal cells were positive for CD68 (e) and TP (d). Some of these cells had abundant cytoplasm and some had dendritic cytoplasm. There were only a few S100 protein-positive cells among lymphoma cells (e). The glandular epithelial cells expressed iNOS (f).
Fig. 2. A case of DLBL. a) H.E. b) CD21. c) CD68. d) Anti-TP. e) Anti-S100 protein. f) Anti-iNOS. Large lymphoma cells showed diffuse proliferation (a). A destroyed meshwork of CD21-positive FDC was remarkable in parts (b). Many CD68-positive or TP-expressing cells were noted (c, d). Some of these cells had abundant cytoplasm and were positive for CD68 and TP, whereas dendritic cytoplasm of these cells was labeled only by TP (d). There were a few S100 protein-positive cells (e). Expression of TP was not recognized in these lymphoma cells and stromal cells (f).
were positive for CD79a. Some CD68-positive cells and TP-positive cells were seen among lymphoma cells in the mucosa. A few cells having rich cytoplasm were positive for CD68 and TP. Some of these cells had CD68-positive or TP-positive dendritic cytoplasm. Only a few S100 protein-positive cells were found. The glandular epithelial cells expressed iNOS, whereas no stromal cells expressed iNOS among the lymphoma cells.

In the case of DLBL (Fig. 2), a diffuse proliferation of large lymphoma cells was found. These lymphoma cells were positive for CD79a and negative for CD3 and CD5. A destroyed meshwork of CD21-positive FDC was remarkable in this case. Among lymphoma cells, many CD68-positive cells were seen. In most CD68-positive cells the dendritic cytoplasm was labeled by the anti-TP antibody. A few S100 protein-positive cells were seen. There were no cells expressing iNOS in this case.

The numbers of gBL cases with an increase of stromal cells labeled by each of anti-CD68, anti-CD21, anti-S100 protein, anti-TP and anti-iNOS antibodies are listed in Table 2. Many CD68-positive stromal cells intermingled among lymphoma cells in many cases of MALT type (9 of 11 cases) and DLBL (22 of 23 cases) and had abundant cytoplasm (Figs. 1c, 2c). Some of the CD68-positive cells had dendritic cytoplasm (Figs. 1c, 2c). Residual CD21-positive FDC were recognized in the areas without obvious GC only in two cases of DLBL (Fig. 2b). S100 protein-positive stromal cells were also seen in one each case of MALT type and DLBL. And the CD68-positive stromal cells having abundant cytoplasm expressed TP in their cytoplasm and also in dendritic cytoplasm in most cases of MALT type (8 of 11 cases) and in DLBL (17 of 23 cases). The TP-positive stromal cells formed an ill-defined loose meshwork in the background (Figs. 1d, 2d). There were few stromal cells expressing iNOS in DLBL (Fig. 2f). But in MALT type, a few cells expressed iNOS in one case and glandular epithelial cells expressed iNOS in two cases (Fig. 1f).

Changes of GC in the gBL are listed in Table 3. Typical early and developed colonization of lymphoma cells was noted only in MALT type. Developed colonization of lymphoma cells in the case of MALT type is presented in Fig. 3. Expansive growth of lymphoma cells to the extra-GC areas was recognized as a corona of the lymphoma cells (Fig. 3a) and associated with the ill-defined meshwork formation of TP-positive DC (Fig. 3d). In the colonization of lymphoma cells, expression of iNOS (Fig. 3f) was found in three of four cases. The CD21-positive FDC defined GC (Fig. 3b) and expressed S100 protein (Fig. 3e).

Unusual GC colonization of lymphoma cells was noted in two DLBL (Table 3). One showed an angiofollicular pattern. The other associated many T-cells (Fig. 4). In the diffuse proliferation of lymphoma cells with ulceration, several lymph follicles were noted in the submucosal areas (Fig. 4a). These follicles included many CD3-positive T-cells (Fig. 4b). The meshwork of CD21-positive FDC defined these follicles (Fig. 4c). These GC associated CD79a-positive lymphoma cells and small to medium-sized B-cells (Fig. 4d). In these GC there were some CD68-positive cells and

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**Table 2. Immunological phenotype of the stromal cells**

<table>
<thead>
<tr>
<th></th>
<th>CD68</th>
<th>CD21</th>
<th>S100</th>
<th>TP</th>
<th>iNOS</th>
</tr>
</thead>
<tbody>
<tr>
<td>MALT type (11 cases)</td>
<td>9</td>
<td>0</td>
<td>1</td>
<td>8</td>
<td>3</td>
</tr>
<tr>
<td>DLBL (23 cases)</td>
<td>22</td>
<td>2</td>
<td>1</td>
<td>17</td>
<td>0</td>
</tr>
</tbody>
</table>

TP: Anti-thymidine phosphorylase antibody.
iNOS: Anti-inducible nitric oxide synthase antibody.
#1: In two cases, an obvious increase of epithelial cells expressing iNOS was noted.

**Table 3. Changes of germinal centers in gastric B-cell lymphoma**

<table>
<thead>
<tr>
<th>Change of germinal centers</th>
<th>No. of cases with each change of germinal centers in MALT type (11 cases)</th>
<th>in DLBL (23 cases)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Germinal center colonization</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>Early phase</td>
<td>1 (1)</td>
<td>0</td>
</tr>
<tr>
<td>Developed</td>
<td>3 (2)</td>
<td>0</td>
</tr>
<tr>
<td>Angiofollicular</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>With many T-cells</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Destroyed germinal center with destructive invasion of lymphoma cells</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Residual lymph follicles</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

( ): No. of cases expression of iNOS was recognized in the germinal centers.
Fig. 3. Germinal center colonization in a case of MALT type. a) H.E. b) CD21. c) CD68. d) Anti-TP. e) Anti-S100 protein. f) Anti-iNOS. A developed germinal center colonization showed a dark central area, a corona of lymphoma cells, and marginal cuffing of small lymphocytes (a). In the central area, a meshwork of CD21-positive FDC was recognized (b). These FDC were also positive for S100 protein (e). Many CD68-positive macrophages and dendritic cells were seen in the central area and in the corona of the lymphoma cells (c). In the corona of the lymphoma cells, an ill-defined meshwork of TP-positive dendritic cytoplasm of DC was seen (d). In the central area and in the corona of the lymphoma cells, some stromal cells expressed iNOS (f).
Fig. 4. Unusual germinal centers in a cases of DLBL. a) H.E. b) CD3. c) CD21. d) CD79a. e) CD68. f) Anti-TP. In the diffuse proliferation of lymphoma cells with ulceration, several lymph follicles were noted (a). These follicles included many CD3-positive T-cells (b). But the meshwork of CD21-positive FDC defined these follicles (c) and associated CD79a-positive lymphoma cells and small to medium-sized B-cells (d). In these germinal centers there were some CD68-positive cells (e) and many TP-positive DC forming an ill-defined meshwork (f). Therefore, these unusual lymph follicles were evaluated as unusual germinal center colonization with many T-cells (Table 3).
IV. Discussion

Based on the paraffin-immunohistochemistry, the gBL cases examined were of CD5-negative post-GC B-cells [25], although mantle cell lymphoma [7, 24, 33, 36], of which lymphoma cells were positive for CD5, exists in the gastrointestinal tract and manifests so-called lymphomatoid polyposis [13, 28, 34, 37, 46, 52–54].

The cases of gBL in this study were of Chinese origin, and infection of HP could not be evaluated only in the representative sections of each case. However, we looked these Chinese gBL cases as HP-related ones because of the prevalence of HP infection in China [21]. We also tried to identify HP infection in 21 cases of stomach resected because of gastric or duodenal ulcers in the northeast part of China. Although the surface portion of the gastric mucosa was lost in 4 cases, HP infection was recognized in 15 (88%) of 17 cases. Then, we speculated that the HP infection in the stomach was prevalent in the northeast part of China.

In these Chinese cases of gBL, there was one case of MALT type with cytomegalovirus inclusion disease (CMD) and three cases of DLBL with giant lymphoma cells. Because in-situ hybridization analysis of Epstein-Barr virus infection [18] and direct DNA sequencing analysis of the immunoglobulin heavy chain gene variable region [19] did not show obvious differences between these Chinese gBL cases and the reported gBL cases in the other areas, the authors looked these Chinese cases as common cases of gBL.

Co-existence of lymphoma cells and stromal cells was reported in lymphoepithelial lymphoma of T-cell type [51], suggesting that both lymphokines from lymphoma cells and cytokines from epithelioid cells supported the proliferation of each other [3, 23, 29, 30, 35, 38, 48, 49, 58]. As the one example of the co-existence of lymphoma cells and stromal cells, we elucidated the meshwork formation of TP-positive DC in mature T-cell neoplasm [16]. Lymphokines of T-cells can induce TP on fibrocyte- or DC-like synovial cells [6, 57]. This study indicated the co-existence of CD68-positive cells, an ill-defined loose meshwork of TP-positive DC, and intermingling T-cells with lymphoma cells in gBL (Table 2). Because CD68-positive cells had abundant cytoplasm and dendritic cytoplasm (Figs. 1c, 2c), TP-positive DC seemed to derive from CD68-positive cells and may be stimulated by the intermingling T-cells. Most of the intermingling T-cells in MALT type lymphoma were reported to be CD45RO+ memory cells [31]. Histogenesis of the unusual GC in a case of DLBL (Fig. 4) explained the relationship among T-cells, CD68-positive cells and TP-positive DC. In the GC where CD79a-positive lymphoma cells and small to medium-sized B-lymphocytes proliferated with the background of meshwork of CD21-positive FDC, the infiltrated T-cells stimulated CD68-positive cells to differentiate to TP-positive DC. It was reported that activated CD69+ helper T cells in lymph follicles probably stimulated B-cells in the mucosa with HP infestation [56]. The ill-defined meshwork of TP-positive DC was seen as preparing a microenvironment to transform small to medium-sized lymphocytes to the lymphoma candidate cells.

On the other hand, we speculated that Lewis X and Y in HP bodies induced iNOS in the GC of regional lymph nodes [20]. NO synthesized by the iNOS gave rise to disordered B-cell immunity against HP. The disordered anti-HP B-cell immunity caused hyperplasia of MALT and MALT type lymphomagenesis. On-going somatic hypermutation of the IgH gene variable region in MALT type lymphoma might be explained by the disordered antigen recognition in the NO-rich microenvironment [19]. As for T-cells in HP infection, dominant th1 T-cells [4], loss of TCRBV611B function [32], oligoclonal expansions of T-cell repertoire [12], and highly variable T-cell responses to 60-kilodalton heat shock protein (HSP60) [50] were reported in HP infection. Expression of iNOS was also found in stromal cells in the paracortex of the regional lymph nodes in the stomach with HP infection [20]. Therefore, these reports suggested disordered T-cell immunity in HP infection.

This study indicated expression of iNOS in GC with colonization of lymphoma cells (Fig. 3f) and in glandular epithelial cells of the mucosa in MALT type gBL (Fig. 1f). Because MALT type gBL transforms to DLBL through GC colonization and maintains proliferation of its lymphoma cells in the mucosa [25], NO supplied to the GC and in the mucosa was thought to be a kind of growth and transforming factor of MALT type gBL. But it is unknown what induced iNOS in the GC and in the glandular epithelial cells in MALT type lymphoma. Expression of iNOS was seen in the GC located in the mucosa with the MALT type but not in the unusual GC in the submucosal layer with DLBL in this study; HP infection in the mucosa may have indirectly induced iNOS, even after the outcome of MALT type lymphoma. Prognostic factors of MALT type lymphoma after eradication of HP infection are reported to be an assessment of deep submucosal invasion by endosonography [43], monoclonal B-cell population [5], t(11;18)(q21;q21) translocation [39, 44], alteration of p53 gene [22] and CagA strains of H. pylori [9, 10]. Recently, expression of MUC-1 mucin and its disappearance in GC in MALT type gBL was reported in follicular DC in the reactive lymphoid hyperplasia [55], suggesting that the disappearance of MUC-1 mucin in follicular DC in MALT predicts occurrence of MALT type gBL. This study suggested that iNOS expression in the GC with lymphoma cell colonization and in the glandular epithelial cells is also a prognostic factor.

This study also suggested that the ill-defined loose
meshwork of DC expressing TP and NO-rich microenvironment were the factors which promoted growth and transform of HP-related cases of gBL, as shown in Fig. 5. Based on lymphocytic traffic among the pools in the lymph nodes, the peripheral blood and tissue [2], CD4 and CD8 T-cells and subpopulation of B-cells re-circulated among the pools, whereas the other subpopulation of B-cells and gamma/delta T-cells did not. In the HP infection, anti-HP T- and B-cell immunity and the related antigens such as HSP60 could be observed in the lymphocytic pools in the gastric mucosa with lymphoma tissue, the regional lymph nodes, and the peripheral blood. Then, in the early and late phases of MALT type lymphomagenesis, disordered anti-HP T- and B-cell immunity was thought to play a role in maintaining MALT type lymphoma. Helper T-cells in anti-HP T-cell immunity probably induced TP in DC. NO-rich microenvironment was induced indirectly by LPS of HP body [20]. Thus, these two stromal factors in HP-related cases of

Fig. 5. Conceptual relation among HP infection, lymphocytic traffic, oncogenesis and histogenesis of MALT type and DLBL in the stomach. HP-related antigens are processed in the regional lymph node and anti-HP T and B-cell immunity is established. But HP-body’s lipopolysaccharides (LPS) deposit in stromal cells in the paracortex and in the germinal centers (GC) and induce inducible nitric oxide (iNOS). Nitric oxide (NO) synthesized by the iNOS makes the anti-HP T- and B-cell immunity disordered. The T-cells and B-cells in the anti-HP immunity migrate to the stomach from the lymphocyte pool in peripheral blood. The anti-HP disordered immunity evokes hyperplasia of MALT. Candidate cells of MALT type lymphoma cells may traffic through the peripheral blood pools to the stomach. In the stomach the candidate cells proliferate as MALT type lymphoma, depending on the co-existence of intermingling T-cells, CD68-positive stromal cells and TP-expressing dendritic cells (DC), in the NO-rich microenvironment. In the mucosa MALT type lymphoma cells probably traffic among the mucosa and the MALT tissue. In the GC with NO-rich microenvironment, MALT type lymphoma cells might gain genetic alternation and transform to those of DLBL. In the DLBL, proliferation of lymphoma cells might be depend on the co-existence of intermingling T-cells, CD68-positive stromal cells, and TP-expressing DC.
gBL were stopped by anti-HP therapy and it was the most effective part of the unknown mechanism of anti-HP therapy effective for gBL. The NO-rich GC in the regional lymph nodes and the NO-rich microenvironment in the MALT type gBL tissue were thought to be the place where genetic alterations, such as t(11;18)(q21;q21), translocation [5, 44] and the alteration of p53 gene [39] occurred in the low grade MALT type lymphoma cells.

V. Acknowledgments

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