

## ***Helicobacter pylori* and the t(11;18)(q21;q21) Translocation in Gastric Low-grade B-Cell Lymphoma of Mucosa-associated Lymphoid Tissue Type**

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The reported regression of mucosa-associated lymphoid tissue (MALT) type gastric low-grade B-cell lymphoma following treatment for *Helicobacter pylori* (*H. pylori*) infection has not yet been comprehensively analyzed, especially in relation to the recently identified *c-IAP2-MALT1/MLT* gene alteration resulting from the t(11;18)(q21;q21) chromosomal translocation found in MALT lymphoma. The relationship between MALT lymphomas and *H. pylori* was investigated in 30 patients who received an antibacterial treatment. Patients were followed up by means of endoscopy and biopsy. Molecular genetic analyses focused on the presence or absence of the immunoglobulin heavy chain (IgH) gene and/or *MALT1/MLT* gene alteration resulting from t(11;18)(q21;q21) translocation. *H. pylori* was positive in 26 of the 30 patients. The overall success rate of cure of *H. pylori* infection was 96% (25/26). Thirteen patients (52%) showed complete remission (CR) of lymphoma, nine (36%) partial remission (PR), and three (12%) registered no change (NC). Statistical analysis revealed significant differences between CR and PR/NC patients in age (<60 or 60), in lymphoma location (single or multiple sites) and in the presence or absence of gene rearrangement before eradication ( $P < 0.05$ ). Endoscopy showed a cobblestone appearance only in PR cases and polypoid features predominantly in NC cases. Two NC patients with polypoid gross appearance showed rearrangements involving either *c-IAP2* or *MALT1* gene in Southern blot analysis, while none of seven other resected patients with non-polypoid superficial gross appearance showed rearrangement. Gastric MALT lymphoma could be pragmatically subdivided into three groups, CR (MALT-A), PR (MALT-B), and NC (MALT-C) on the basis of the reaction to eradication of *H. pylori*. We speculate that MALT-A may represent an incipient neoplasm or dysplasia, MALT-B a neoplasm activated by antigenic stimulation of *H. pylori*, and MALT-C a lymphoma independent of *H. pylori*. Polypoid lesions in MALT-C were associated with *c-IAP2-MALT1/MLT* gene alteration resulting from t(11;18)(q21;q21). This classification is thought to be clinically significant for deciding the most appropriate mode of treatment of MALT-type lymphoproliferative disorders.

Key words: MALT lymphoma — *Helicobacter pylori* — t(11;18)(q21;q21) — Translocation — *MALT1*

It has been well documented that the stomach is one of the commonest sites for low-grade B-cell lymphoma of mucosa-associated lymphoid tissue (MALT) type to arise, although lymphoid tissue is absent in the normal stomach. However, MALT commonly develops in the stomach as a result of the reaction to infection with *Helicobacter pylori*. This type of tissue may have an autoimmune component, and this seems to be a prerequisite for the development of low-grade gastric lymphoma.<sup>1)</sup> Indeed, a close association has recently been indicated with the presence of certain strains of *H. pylori* found in more than 90% of patients with gastric MALT lymphomas.<sup>1,2)</sup> The histologic features of the latter resemble those of acquired MALT, which in severe *Helicobacter*-associated chronic gastritis can

closely simulate lymphoma.<sup>1,3)</sup> In fact, the two conditions overlap and this may make it impossible, especially in biopsy specimens, to distinguish severe gastritis from a low-grade gastric lymphoma, although demonstration of B-cell monoclonality by either immunocytochemical or molecular methods may be helpful.<sup>4)</sup>

In general, MALT lymphomas are not widely disseminated at the time of diagnosis and good survival may be achieved following surgical excision.<sup>1)</sup> Since the first report of regression after eradication of *H. pylori* by Wotherspoon *et al.*, various studies have dealt with this issue.<sup>5,6)</sup> The data support the conclusion that the growth of low-grade gastric MALT lymphoma is influenced by *H. pylori*, and high remission rates after eradication therapy have been confirmed.<sup>6–11)</sup> Recent studies including ours have shed light on the pathogenesis of MALT lymphomas. They are often associated with a characteristic translocati-

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tion, t(11;18)(q21;q21), resulting in the *c-IAP2-MALT1/MLT* fusion transcript. However, the clinical, endoscopic, histological and molecular genetic characteristics of the response of gastric MALT lymphoma to *H. pylori* eradication have not been comprehensively analyzed.

The aim of this study was to identify varieties of MALT lymphomas and to examine their different relations to *H. pylori* infection and its eradication. We also examined the relationship between the response of MALT lymphoma to eradication therapy and the *c-IAP2-MALT1/MLT* gene alteration by using a probe that we recently identified.<sup>12)</sup>

## MATERIALS AND METHODS

**Diagnosis and staging of MALT lymphoma** From October 1993 to April 1998, 30 patients (16 women, 14 men, mean age 60.6 years, range 38 to 83 years) with localized low-grade B-cell gastric MALT lymphomas were included in this prospective unicenter study. All MALT lymphomas were pathologically diagnosed by examination of endoscopic biopsy specimens by two or more pathologists in our hospital. Five to eight biopsy specimens were randomly obtained from any abnormal area of the stomach in every upper gastrointestinal endoscopy. Another two to four specimens were obtained from endoscopically normal areas of the stomach for the evaluation of the location and spreading of MALT lymphoma. The diagnosis of atypical lymphoid infiltration was made when lymphoid infiltration had led to atrophy of the gastric glands, with parafollicular proliferation of centrocyte-like cells, while lymphoepithelial destruction was required to confirm the diagnosis of lymphoma. All cases were histologically diagnosed as low-grade MALT lymphoma. Partial inclusion of high-grade components was seen in biopsied specimens of four cases and the resected specimen of one case. Eight cases initially diagnosed as grade 3 in our histological scoring system for the diagnosis of gastric MALT lymphoma, which consists of a minor modification of the system described by Wotherspoon *et al.*, revealed atypical lymphoid infiltration characterized by the parafollicular proliferation of centrocyte-like cells and atrophy of the gastric glands. Despite little evidence of lymphoepithelial lesions, these findings were interpreted as strongly suggesting low-grade MALT lymphoma, so that the patients were included in this study. The degree of the disease was classified according to Musshoff's modification of the Ann Arbor classification,<sup>13)</sup> which defines stage IE as a process limited to the stomach and stage IIE as a process with adjacent involvement (IIE1). Staging involved clinical examinations, ultrasonography of the abdomen, endosonography, computed tomography of the abdomen and thorax, gallium scan and bone marrow biopsy. Twenty-nine cases were staged as IE and only one case as IIE1.

**Assessment and eradication of *H. pylori*** *H. pylori* infection was investigated in all cases by means of culture of endoscopic biopsy specimens obtained from the greater curvature of the gastric antrum and from the upper gastric body. Serum anti-*H. pylori* immunoglobulin G (IgG) antibody titers were measured by means of an enzyme linked immunosorbent assay using GAP-IgG (Biomerica Inc., Newport Beach) until the end of June 1996 and HM-CAP (Epi Inc., New York) since then. Antibiotics plus a proton pump inhibitor were administered to 28 of the patients. The first line drugs were: roxithromycin, 300 mg twice daily, plus omeprazole, 20 mg once daily for 2 weeks for 8 patients; clarithromycin, 200 mg twice daily, plus metronidazole, 500 mg twice daily for one week, with omeprazole, 20 mg once daily for 2 weeks, for 13 patients; clarithromycin, 200 mg twice daily, amoxicillin, 500 mg thrice daily, plus omeprazole, 20 mg, or lansoprazole, 30 mg once daily for 2 weeks, for seven patients. Treatment began immediately after diagnosis of *H. pylori* infection. After 6 or 8 weeks, culturing of biopsy specimens and a <sup>13</sup>C-urea breath test were performed to evaluate the results. The treatment was considered successful for the patients who showed negative results in both examinations.

**Evaluation of the reaction of MALT lymphoma to eradication of *H. pylori*** Upper gastrointestinal endoscopy with biopsy for re-evaluation of MALT lymphoma was performed every 3 to 6 months after treatment for *H. pylori* infection. Histologic responses were graded according to our histological gastric MALT lymphoma scoring system described above. Grade 3 in post-treatment biopsy samples was defined as partial depletion of atypical lymphoid cells from the tunica propria of focal lymphoepithelial destruction. Complete regression of the tumor was defined as post-treatment biopsy samples showing none of the prediagnosed atypical lymphoid cell infiltrations, and the tunica propria being completely depleted of lymphoid cells, as is common after chemotherapy. Complete remission (CR) of the lesion was also endoscopically documented. Partial remission (PR) was defined as improvement of endoscopic findings or histology following cure of *H. pylori* infection. In practice, the PR patients showed apparent regression in terms of the gross appearance of the tumor. Their post-treatment biopsy samples revealed the tunica propria to be partially depleted of lymphoid cells, but with focally persistent infiltration of atypical lymphoid cells resulting from lymphoepithelial destruction. No change (NC) was the equivalent of a post-treatment score of 4 or more and an unchanged endoscopic appearance.

**Molecular genetic analysis** Rearrangements of the immunoglobulin heavy chain genes in biopsy specimens taken from the lesions before and after eradication treatment were examined by means of the polymerase chain reaction (PCR) and Southern blot hybridization. In prac-

tice, there was no discrepancy between the results of the two methods except in one case, which was judged positive. Digestion was performed to completion with restriction enzymes, and <sup>32</sup>P-labeled probes for the immunoglobulin (Ig) heavy chain-joining region were used for hybridization. PCR amplification of the CDR2 and CDR3 regions was performed on high-molecular-weight DNAs extracted from fresh-frozen gastric biopsy samples with the aim of detecting monoclonal B-cell proliferation by using primers specific for the framework regions FR2a and FR3a, as described previously.<sup>14</sup> The chromosomal translocation t(11;18)(q21;q21) was analyzed by Southern blot hybridization with *c-IAP2* cDNA and *MALT1* genomic probes. The *c-IAP2* cDNA probe was made by RT-PCR with total RNA of peripheral blood mononuclear cells using a primer pair which was designed to amplify its coding sequence.<sup>15</sup> These primers are 5'-ATG AAC ATA GTA GAA AAC AGC ATA TTC-3' and 5'-TCA TGA AAG AAA TGT ACG AAC TG-3'. The *MALT1* H/R 3.6 kb genomic probe has been shown to detect gene rearrangement in some MALT patients with t(11;18)(q21;q21).<sup>12</sup> Human placental DNA was used as control DNA. The resected stomachs of seven patients with gastric low-grade B-cell lymphoma of MALT type, of which the macroscopic appearance showed non-polypoid superficial type with stage IE or IIE1, were also examined. These materials had been obtained before the first report of Wotherspoon *et al.*<sup>1</sup> dealing with the regression of gastric MALT lymphoma following cure of *H. pylori* infection, and were examined instead of the biopsy specimens of the CR and PR patients, because they were too small in amount for molecular analysis.

**Statistical methods** The Wilcoxon test was used to compare the means for continuous variables between groups with the results expressed as means and standard deviation (SD). Associations between categorical variables were evaluated with the  $\chi^2$  test and Fisher's exact test. Two-sided *P* values of 0.05 or less were considered to indicate statistical significance.

**RESULTS**

**Clinical, endoscopic, histological and molecular genetic findings and follow-up results of the 25 cases of successful eradication of *H. pylori*** Fig. 1 shows the outcomes of all cases. *H. pylori* was evaluated positive in 26 cases and negative in four. Cures were achieved for 25 *H. pylori*-positive patients (96.1%). The mean follow-up period was 18.2 months, ranging from 3 to 53 months after the eradication treatment. Thirteen patients (52%) showed CR of their lymphomas, nine (36%) PR and three (12%) NC. Table I summarizes clinical, endoscopic, histological and molecular genetic data for the 25 patients in whom cure of *H. pylori* infection was successful. The

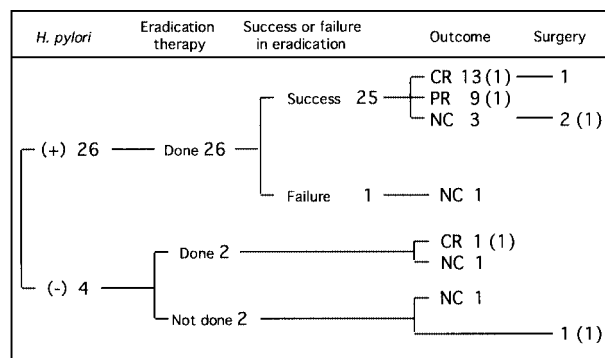


Fig. 1. Outcome of all patients. The numbers in parentheses show the numbers of the cases with high-grade components.

mean follow-up period stands at 18.2 months (range 3–53 months). The median time from cure of *H. pylori* infection to CR for the 13 patients was 3 months (mean 4.9±3.5 months, range 1–12 months). The median period of continuous CR for these patients was 9 months (mean 12±12.7 months, range 0–44 months). No recurrence was detected in CR cases during the follow-up. The median period of PR for the nine cases was 21 months (mean 23.1±13.0 months, range 6–42 months). The median period of no change for the remaining three cases was 4 months (mean 6.3±1.5 months, range 3–12 months). It should be noted that the PR cases (mean 64.7 years) were significantly older than the CR cases (mean 55.9 years) (*P*<0.05, Wilcoxon test). Location and spreading of MALT lesions were evaluated on the basis of the endoscopic and histopathologic findings. In the CR cases, the lesions were generally limited to the gastric body, whereas those of PR and NC cases were distributed over two or more sites of the stomach. The endoscopic gross appearances of gastric MALT lymphomas were classified into several types, i.e., multiple ulcers, mucosal erosions, ulcers or erosions with a cobblestone appearance, discolored mucosa, superficial depressed gastric carcinoma-like and polypoid mass. The endoscopic findings for each case were recorded in terms of one or more of these appearances. It is noteworthy that cobblestone appearance was detected in PR cases only. Polypoid mass was seen in two (67%) of three NC cases, but in only one (8%) of thirteen CR cases. The histological scoring before eradication identified grade 3 tumors exclusively in CR cases.

With regard to rearrangement of IgH before and after eradication, only the germline was detected in all CR cases examined during a median period of 4 months (mean±SD 6.8±5.3 months, range 2–17 months). A rearranged band was detected before and after eradication in four (67%) of six PR cases and the germline in only one (17%) during the entire clinical course. In only one PR

Table I. Clinical, Endoscopic, Histological and Molecular Genetic Data for 25 Patients with Low-grade B-Cell Gastric Lymphoma of MALT Type Who Showed Cure of *Helicobacter pylori* Infection after Eradication Therapy

Parameters	Lymphoma response to eradication of <i>H. pylori</i>		
	Complete remission (CR)	Partial remission (PR)	No change (NC)
<i>n</i> (Total 25)	13	9	3
Female/male	7/6	4/5	1/2
Age (years)	55.9 (38–76)	64.7 (45–77)	58
Mean duration of follow-up (months)	17.9 (3–53)	23.1 (6–42)	6.3
Location of lesions			
Fundus	0	1	0
Body	11	3	0
Fundus-body	1	1	2
Body-antrum	0	3	0
Fundus-body-antrum-duodenum	0	1	1
Antrum-duodenum	1	0	0
Endoscopic appearance			
Multiple ulcers	5	6	0
Mucosal erosions	4	3	1
Ulcers or erosions with a cobblestone appearance	0	4	0
Discolored mucosa	3	2	2
Superficial depressed gastric carcinoma-like	2	3	0
Polypoid mass	1	0	2
Histological scoring before/after eradication			
3/1	3	0	0
3/2	5	0	0
5/1	3	0	0
5/2	2	0	0
4/4	0	1	0
5/3	0	6	0
5/4	0	1	0
5/5	0	1	3
Rearrangement of IgH before/after eradication			
G/G	9	1	0
R/G	0	1	0
R/R	0	4	2

G, germline; R, rearrangement.

case, a rearranged band was not seen after cure of *H. pylori* infection. In these PR cases, rearrangement of IgH was investigated during a median period of 20 months (mean±SD 18±3.9 months, range 11–23 months). A rearranged band was detected before and after eradication in both NC cases during a median period of 4.5 months (mean±SD 4.5±1.5 months, range 3 and 6 months). The two cases with high-grade components (one CR and one PR case shown in Fig. 1) could not be examined because of sampling errors.

The results were statistically analyzed by grouping the patients according to sex, age, location of the lesion, endoscopic gross appearance and the presence or absence of rearrangement before eradication. These results and group-

ings are summarized in Table II. Statistically significant differences between CR patients and both PR and NC (PR/NC) patients were detected in age (<60 or 60), in location of the lesion (single or multiple sites) and in the presence or absence of gene rearrangement before eradication ( $P<0.05$  according to Fisher's exact test). No significant differences in results were detected in terms of sex. Cobblestone or polypoid gross appearances were associated with PR/NC cases, but not significantly so, probably due to the limited number of cases in the present study.

Of the three patients with NC, two were finally referred for total gastrectomy (cases 2 and 3 shown in Table III). Their resected specimens revealed low-grade lymphoma with and without high-grade components, and the latter

Table II. The Relationship between Variables (Sex, Age, Location, Endoscopic Findings and Rearrangement of IgH before Eradication) and Reaction to Cure of *H. pylori* Infection (CR, PR and NC)

Variable	Category	CR	PR/NC	<i>P</i> <sup>a, b)</sup>
Sex	Male	6	7	0.581 <sup>a)</sup>
	Female	5	9	
Age	<59	8	6	0.071 <sup>b)</sup>
	60≤	3	10	
Location	Single area	9	6	0.022 <sup>b)</sup>
	Multiple area	2	10	
Endoscopic findings	Cobblestone or polypoid	1	6	0.398 <sup>b)</sup>
	Others	12	22	
Rearrangement of IgH before eradication	G	9	1	0.0004 <sup>b)</sup>
	R	0	7	

a)  $\chi^2$  test.

b) Fisher's exact test.

G, germline; R, rearrangement; CR, complete remission; PR, partial remission; NC, no change.

Table III. Surgically Resected Cases of MALT Lymphoma

Case	Age	Sex	Endoscopic appearance	<i>H. pylori</i>	Outcome following cure of <i>H. pylori</i>	Interval between eradication and surgery (months)	Depth of invasion	Lymph-node involvement	High-grade component	Coincident lesion	Outcome after resection	Southern blot analysis	
												Ig heavy chain	<i>MALT1</i> gene
1	60	F	Multiple ulcers & erosions	+	CR	5	Impossible to evaluate	-	-	Signet ring cell carcinoma limited to the mucosal tissue	Alive without disease for 26 weeks	ND	ND
2	39	M	Polypoid mass & discolored areas	+	NC	12	Submucosal tissue	-	-	-	Alive without disease for 24 weeks	R	R
3	72	F	Polypoid mass & multiple erosions	+	NC	3	Subserosal tissue	+	+	-	Alive without disease for 18 weeks	R	R
4	60	M	Polypoid mass & lesions like early gastric cancer	-	Eradication was not done		Subserosal tissue	-	+	-	Alive without disease for 19 weeks	ND	ND

CR, complete remission; PR, partial remission; NC, no change; R, rearrangement; ND, not done.

had not been previously observed in gastric biopsy specimens. These patients have been followed up for 18 and 24 months, respectively and no relapse has been observed thus far. Fig. 2 shows an endoscopic picture and histology of case 3.

**The reaction of MALT lymphoma to cure of *H. pylori* infection and the chromosomal translocation t(11;18)(q21;q21)** Gene rearrangement was found in case 2 with the *c-IAP2* probe (Fig. 3A) and in case 3 with the *MALT1* genomic probe (Fig. 3B), indicating that these two cases most likely possess t(11;18)(q21;q21). It is of inter-

est to note that these cases featured polypoid lesions in their gross appearance. In contrast, no rearrangement was identified in the seven controlled cases of which the macroscopic appearances showed non-polypoid superficial type with stage IE or IIE1.

#### DISCUSSION

In the present series, the rate of CR was 52%, that of PR was 36%, and that of NC was 12%, after eradication of *H. pylori*. This CR rate is lower than those reported in pre-

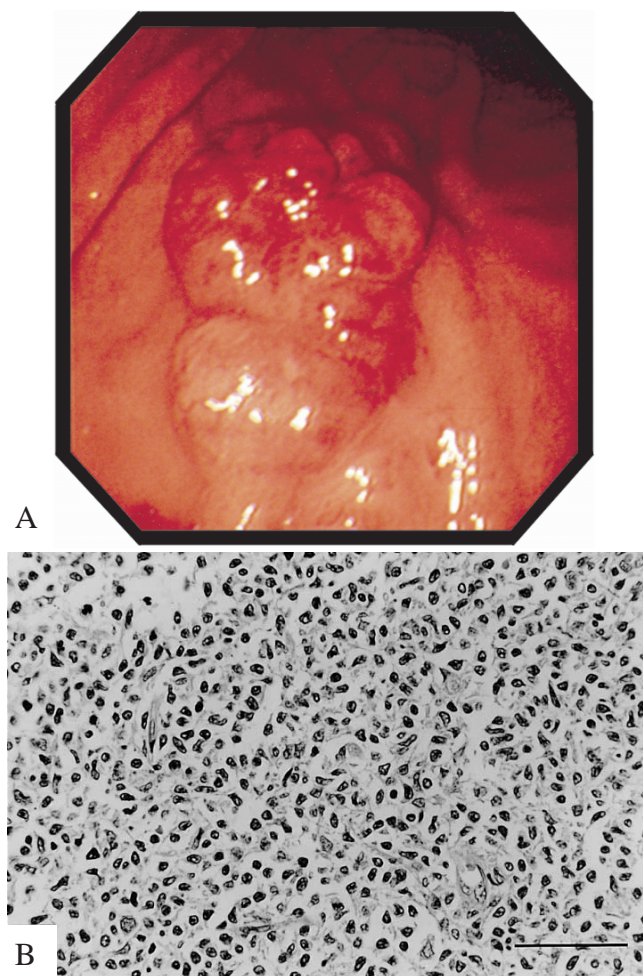


Fig. 2. Case 3 in Table III, with no change after cure of *H. pylori* infection. A: Endoscopy shows a polypoid lesion like a submucosal tumor in the greater curvature of the upper gastric body. This was unchanged after eradication. B: Histology of the resected specimen. Low-grade B-cell lymphoma of MALT type forming lymphoepithelial lesions (LEL) (H&E, original magnification  $\times 100$ , scale bar=60  $\mu\text{m}$ ).

vious studies (54–80%).<sup>6–11,16</sup> We speculate that this might be due to differences between our evaluation and that of others with respect to the histopathology of MALT lymphoma, especially grade 3. In the present study, grade 3 was assessed as suspicion of MALT lymphoma, although other investigators<sup>1,6</sup> have evaluated it as probably reactive. Neubauer *et al.* reported that 22 of 31 patients (71%) continuously showed evidence of monoclonal bands during follow-up, although microscopic analysis did not reveal any evidence of remaining lymphoma.<sup>16</sup> Moreover, Thiede *et al.* recently reported that PCR indicated the persistence of monoclonal B-cells iden-

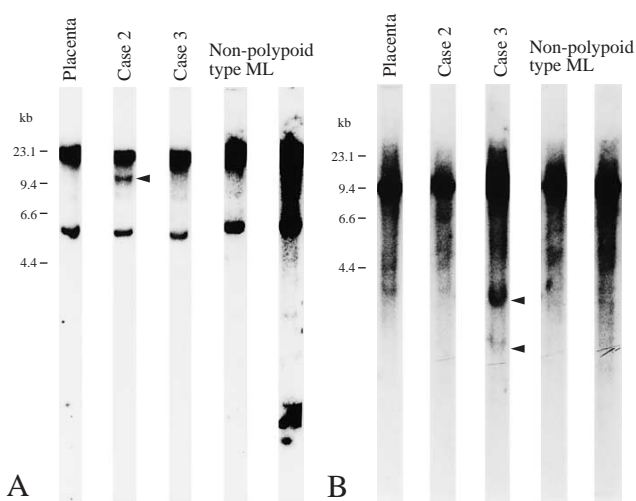


Fig. 3. Southern blot analysis with *c-IAP2* cDNA and *MALT1* genomic probes. Representative results with *Hind*III digestion are shown. The *c-IAP2* cDNA probe demonstrated a rearrangement band in MALT-C case 2 (A), while the *MALT1* H/R 3.6 kb genomic probe revealed rearrangement bands in MALT-C case 3 (B). The arrowheads indicate rearranged bands.

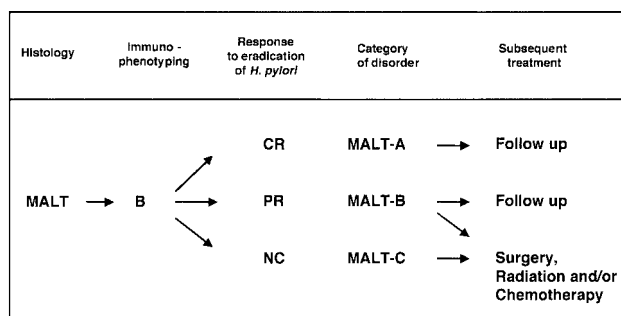


Fig. 4. A pragmatic approach to classification of gastric lymphoproliferative disorders of MALT type. MALT, low-grade B-cell lymphoma of MALT type; B, B-cell phenotype; CR, complete remission; PR, partial remission; NC, no change.

tical or closely related to the lymphoma in about half of all patients obtaining CR after *H. pylori* eradication for up to four years.<sup>17</sup> Their results indicated that histological regression is inconsistent with molecular regression. The lower CR rate of the present study might be the result of our stricter diagnostic criteria, which are supported by the genetic findings.

On the basis of endoscopic, histopathological and genetic analyses, gastric MALT lymphomas can pragmatically be classified into three types (MALT-A, B and C) in terms of their response to *H. pylori* eradication (Fig. 4),

because all CR, PR and NC cases corresponded to, respectively, MALT-A, B and C. MALT-A cases differed from MALT-B and C in that they were younger in age and showed fewer infiltrating sites. MALT-A cases evidenced no rearrangement of IgH during their clinical course, while most MALT-B and C cases showed persistent rearrangement after cure of *H. pylori* infection. Cobblestone and polypoid gross appearances seemed to be characteristic of MALT-B and MALT-C, respectively. We speculate that MALT-A represents an incipient neoplasm (or dysplasia), MALT-B a neoplasm activated by antigenic stimulation of *H. pylori*, and MALT-C a neoplasm independent of *H. pylori*. However, it might be difficult to predict or differentiate these three types before eradication of *H. pylori* infection. Sackmann *et al.* reported that staging of gastric low-grade MALT lymphomas by means of endoscopic ultrasonography allows prediction of the response to therapy for *H. pylori*,<sup>11</sup> but the current study indicated that it was not applicable for predicting the individual responses of MALT lymphoma cases at the same clinical stage to cure of *H. pylori* infection, even though the clinical stage can be assessed by means of endosonography. Indeed, the MALT-C cases in our series had been evaluated as stage IE by endosonography before eradication of *H. pylori* infection. Bayerdorffer *et al.*<sup>16</sup> reported that all of their five patients, who were referred for surgical treatment because of the absence of regression after cure of *H. pylori* infection, showed evidence of high-grade lymphoma in their gastric resection samples, but not in gastric biopsy specimens. However, the resected specimen of one of our cases of MALT-C cases histologically showed a pure MALT type low-grade B-cell lymphoma without any high-grade components, implying that some pure low-grade lymphomas do not regress in spite of eradication of *H. pylori* infection, and indicating that MALT-C cases consist of a low-grade B-cell lymphoma with or without high-grade components. No demonstration of Ig gene rearrangement in the CR group might suggest that those cases are not true lymphoma. However, the distinction between MALT-A and MALT-B from histologic findings was occasionally very difficult. It remains to be clarified whether MALT-A lesion represents "pseudolymphoma" or an incipient neoplasm.

One case without *H. pylori* infection entered CR after the treatment for the infection. In this case, histology of the biopsied specimen taken from unaffected mucosa revealed chronic active gastritis, which was suggestive of *H. pylori* infection. The detection method of *H. pylori* might have given a false negative result due to a low *H. pylori* density.

The chromosomal translocation t(11;18)(q21;q21) has been identified as a recurring chromosomal abnormality in a subset of extranodal marginal zone B-cell lymphoma, a low-grade lymphoma of mucosa-associated lymphoid tis-

sue.<sup>18</sup> We have reported that a YAC clone y789F3 includes the breakpoint at 18q21 in a MALT lymphoma.<sup>19</sup> Subsequently we<sup>12</sup> and Dierlamm *et al.*<sup>20</sup> identified a novel gene, *MALT1/MLT*, at 18q21 involved in t(11;18)(q21;q21) of MALT lymphomas, which was found to be fused to the *c-IAP2* gene involved in an anti-apoptotic signal transduction pathway.<sup>20</sup> Although the probes to detect all of the gene alterations involved in t(11;18)(q21;q21) have not been well established because of heterogeneous breakpoints,<sup>12,20</sup> the present study is the first report dealing with the relationship between the reaction of MALT lymphoma to eradication therapy and *c-IAP2-MALT1* gene alteration. Notably, *MALT1* rearrangements were only observed in polypoid lesions of MALT-C.

In contrast, these genetic events were not observed in the stage IE or IIE1 patients whose macroscopic appearances showed non-polypoid superficial type. We recently reported 8 cases of polypoid gastric MALT lymphoma, the clinicopathologic features of which appeared to resemble closely those of colorectal MALT lymphoma with a polypoid appearance, with little association of *H. pylori* infection in the pathogenesis.<sup>21</sup> Indeed, t(11;18)(q21;q21) was also often observed in MALT lymphoma of the colon and lung.<sup>12,22</sup> These data led to the speculation that the polypoid gastric MALT lymphoma separated from *H. pylori*-dependent non-polypoid tumor is closely associated with *c-IAP2-MALT1/MLT* gene alteration resulting from t(11;18)(q21;q21), and should be categorized together with MALT tumor arising in lung, colon and others with this unique chromosomal translocation. In order to confirm our present findings, it is very important to establish methods to detect any *c-IAP2-MALT1* gene alteration, and this is under investigation in our laboratory, including preparation of a new genomic probe, RT-PCR and antibody production for immunohistochemistry.

We tentatively propose that the strategy for the treatment of MALT lymphoma should be decided according to the following scheme (Fig. 4): follow-up is most appropriate for MALT-A patients, follow-up or surgery for MALT-B patients, and surgery, chemotherapy, radiotherapy or a combination of these for MALT-C patients. It is clinically important to identify the lesions as MALT-A, B or C for deciding the preferred mode of treatment for MALT-type lymphoproliferative disorders. However, the differences among these three types of MALT lymphoma may have to be identified in terms of molecular biology, since it is difficult to differentiate them only histologically, as is done at present.

In conclusion, gastric MALT lymphoma could be pragmatically subdivided into three groups, CR (MALT-A), PR (MALT-B), and NC (MALT-C) on the basis of the reaction to eradication of *H. pylori*. We speculate that MALT-A may represent an incipient neoplasm or dyspla-

sia, MALT-B a neoplasm activated by antigenic stimulation of *H. pylori*, and MALT-C a lymphoma independent of *H. pylori*. Polypoid lesions in MALT-C were associated with t(11;18)(q21;q21). This classification is thought to be clinically significant for deciding the most appropriate mode of treatment of MALT-type lymphoproliferative disorders.

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