

Chromosomal translocation t(11;18)(q21;q21) in gastrointestinal mucosa associated lymphoid tissue lymphoma

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J Clin Pathol 2003;56:36–42

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Accepted for publication
21 August 2002

Aims: To evaluate the chromosomal translocation t(11;18)(q21;q21) in gastrointestinal lymphomas.

Methods: A possible API2–MLT fusion transcript specific to t(11;18)(q21;q21) was examined by means of reverse transcription-polymerase chain reaction (RT-PCR) in tumours from 47 cases of primary gastrointestinal lymphoma (28 low grade mucosa associated lymphoid tissue (MALT) lymphomas, four low grade MALT lymphomas with a high grade component, nine secondary diffuse large B cell lymphomas, four primary diffuse large B cell lymphomas, and two T cell lymphomas).

Results: API2–MLT fusion was seen in four of 28 cases of low grade MALT lymphoma, but it was not seen in other types of lymphoma. Among the low grade MALT lymphomas, the fusion transcript was seen more frequently in colonic tumours than in gastric tumours (two of three compared with two of 24) and in tumours with submucosal invasion than in those confined to the mucosa (four of 13 compared with 0 of 15). *Helicobacter pylori* negative tumours tended to show a higher positive rate than *H pylori* positive tumours (three of six compared with one of 21). None of the gastric tumours that responded to *H pylori* eradication expressed the API2–MLT fusion transcript.

Conclusions: t(11;18)(q21;q21) seems to be one of the genetic alterations related to the development of gastrointestinal low grade MALT lymphoma. Such translocations may be predominantly associated with the development of intestinal MALT lymphoma.

In non-Hodgkin's B cell lymphomas, some specific oncogene rearrangements, which are attributed to chromosomal translocations, have been identified. t(11;14)(q13;q32) is one such translocation characteristic of mantle cell lymphoma, which involves the *bcl-1/cyclin D1* gene at 11q13.¹ Another translocation, t(14;18)(q32;q21), has been detected in 80–90% of follicular lymphomas. This last translocation results in the deregulation and overexpression of the *bcl-2* oncogene.² The *c-myc* gene is known to be rearranged in Burkitt's lymphoma, in association with t(8;14)(q32;q32).³ In addition, the t(3;14)(q27;q32) translocation, which causes deregulation of the *bcl-6* oncogene,⁴ has been implicated in diffuse large B cell lymphoma (DLBCL).

Recently, the t(11;18)(q21;q21) translocation has been shown to be associated with low grade mucosa associated lymphoid tissue (MALT) lymphoma/marginal zone B cell lymphoma.^{5,6} The genes involved in t(11;18)(q21;q21) have been cloned. The 5' partner gene is a member of the evolutionally conserved inhibitor of apoptosis family, apoptosis inhibitor 2 (API2) on chromosome 11, and the 3' partner is a gene of novel function on chromosome 18, which has been designated MALT lymphoma associated translocation (MLT)⁷ or MALT1.^{8,9} The API2–MLT/MALT1 fusion transcript is thought to be specific to t(11;18)(q21;q21). Some investigators have suggested that this chromosomal aberration is associated with intractability to *Helicobacter pylori* eradication treatment in patients with gastric MALT lymphoma.^{10,11} However, the role of t(11;18)(q21;q21) in the pathogenesis of gastrointestinal MALT lymphomas is still unclear.

"Recently, the t(11;18)(q21;q21) translocation has been shown to be associated with low grade mucosa associated lymphoid tissue lymphoma/marginal zone B cell lymphoma"

In our current study, we searched for t(11;18)(q21;q21) in cases of primary gastrointestinal lymphoma by means of a reverse transcription-polymerase chain reaction (RT-PCR) assay for the API2–MLT fusion transcript. The clinicopathological features were compared between patients who were positive and negative for the t(11;18)(q21;q21) translocation, with special emphasis on the importance of this translocation in intestinal MALT lymphoma.

MATERIALS AND METHODS

Patients

Forty seven patients with primary gastrointestinal lymphoma diagnosed at our institutions between October 1993 and September 2001, in whom fresh or frozen tissue samples were available, were enrolled in our study. The patients comprised 26 men and 21 women, ranging in age from 29 to 81 years (mean, 59). The primary sites of lymphoma were as follows: the stomach in 40 patients, the duodenum in two, the ileum in two, and the colon in three. The histology of the lymphoma was graded according to the revised European–American lymphoma classification,¹² with minor modifications as suggested by de Jong and colleagues¹³ and by us.^{14,15} Accordingly, 28 cases were diagnosed as low grade MALT lymphoma (marginal zone B cell lymphoma), four cases as low grade MALT lymphoma with a focal high grade component, nine cases as secondary DLBCL (high grade MALT

Abbreviations: API2, apoptosis inhibitor 2; BIR, baculovirus IAP repeats; DLBCL, diffuse large B cell lymphoma; GAPDH, glyceraldehyde-3-phosphate dehydrogenase; MALT, mucosa associated lymphoid tissue; MLT, mucosa associated lymphoid tissue lymphoma associated translocation; RING, zinc binding RING finger domain; RT-PCR, reverse transcription-polymerase chain reaction

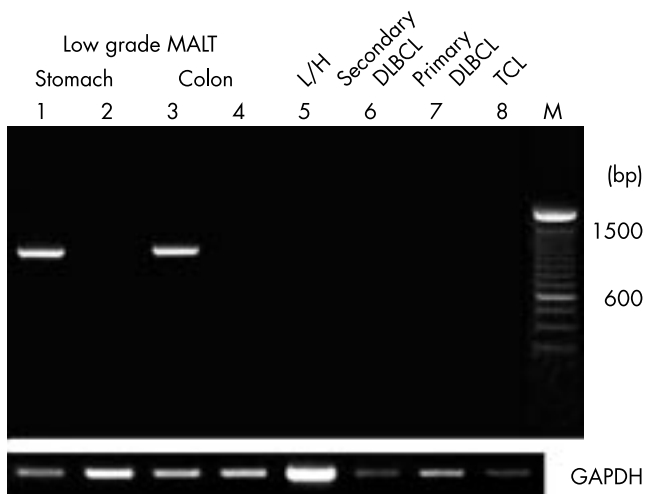


Figure 1 Results of reverse transcription-polymerase chain reaction for API2-MLT fusion transcripts. Lanes 1 (case 23) and 2 (case 5), gastric low grade mucosa associated lymphoid tissue (MALT) lymphoma; lanes 3 (case 27) and 4 (case 28), colonic low grade MALT lymphoma; lane 5, gastric low grade MALT lymphoma with a focal high grade component (L/H); lane 6, secondary gastric diffuse large B cell lymphoma (DLBCL); lane 7, primary gastric DLBCL; lane 8, gastric T cell lymphoma (TCL); lane M, size marker (100 bp). Glyceraldehyde-3-phosphate dehydrogenase (GAPDH), positive internal control.

lymphoma/DLBCL with areas of marginal zone lymphoma¹⁶), four cases as primary DLBCL, and two cases as T cell lymphoma. B cell monoclonality was confirmed in 24 of 28 cases with low grade MALT lymphoma, either by means of PCR for the immunoglobulin heavy chain gene rearrangement (19 cases)¹⁷ or by immunohistochemistry for light chain restriction (five cases).

In 45 patients, the depth of tumour invasion within the gastrointestinal wall was assessed by endoscopic ultrasonography before treatment.¹⁵ In the remaining two patients with primary ileal lymphomas, the depth of invasion was determined on the surgically resected specimens. As a result, 15 lymphomas were considered to be restricted to the mucosa, 16 had invaded the submucosa, five involved the muscularis propria, and 11 reached the subserosa or serosa. According to the Ann Arbor staging system¹⁸ with modifications by Musshoff¹⁹ and Radaszkiewicz and colleagues,²⁰ 23 cases were classified as stage IE₁, four as stage IE₂, nine as stage IIE₁, five as stage IIE₂, two as stage III, and four as stage IV. Thirty six patients were positive for *Helicobacter pylori* and 10 patients were negative, as assessed by histology, culture, rapid urease test, and/or serology. In the remaining one patient, the *H pylori* status was not evaluated.

Thirty three of 47 patients were initially treated to eradicate *H pylori* with a proton pump inhibitor (omeprazole, lansoprazole, or rabeprazole) and a combination of antibiotics (clarithromycin, amoxicillin, and/or metronidazole). Among them, 21 patients underwent eradication treatment alone, four had chemotherapy after eradication, five had surgical resection after eradication, one had radiation after eradication, and two had chemotherapy and surgery after eradication. Ten patients were initially treated by a surgical resection with or without subsequent chemotherapy, and four patients had chemotherapy alone.

RT-PCR

In all 47 patients, total RNA was extracted from the frozen tissue specimens obtained by either endoscopic biopsy or endoscopy/surgery, using the acid guanidium thiocyanate/phenol/chloroform method. Total RNA (1 µg) was reverse transcribed to cDNA using reverse transcriptase (Superscript II; Life Technologies, Tokyo, Japan) and random primers (Life Technologies) in a total volume of 20 µl containing each dNTP.

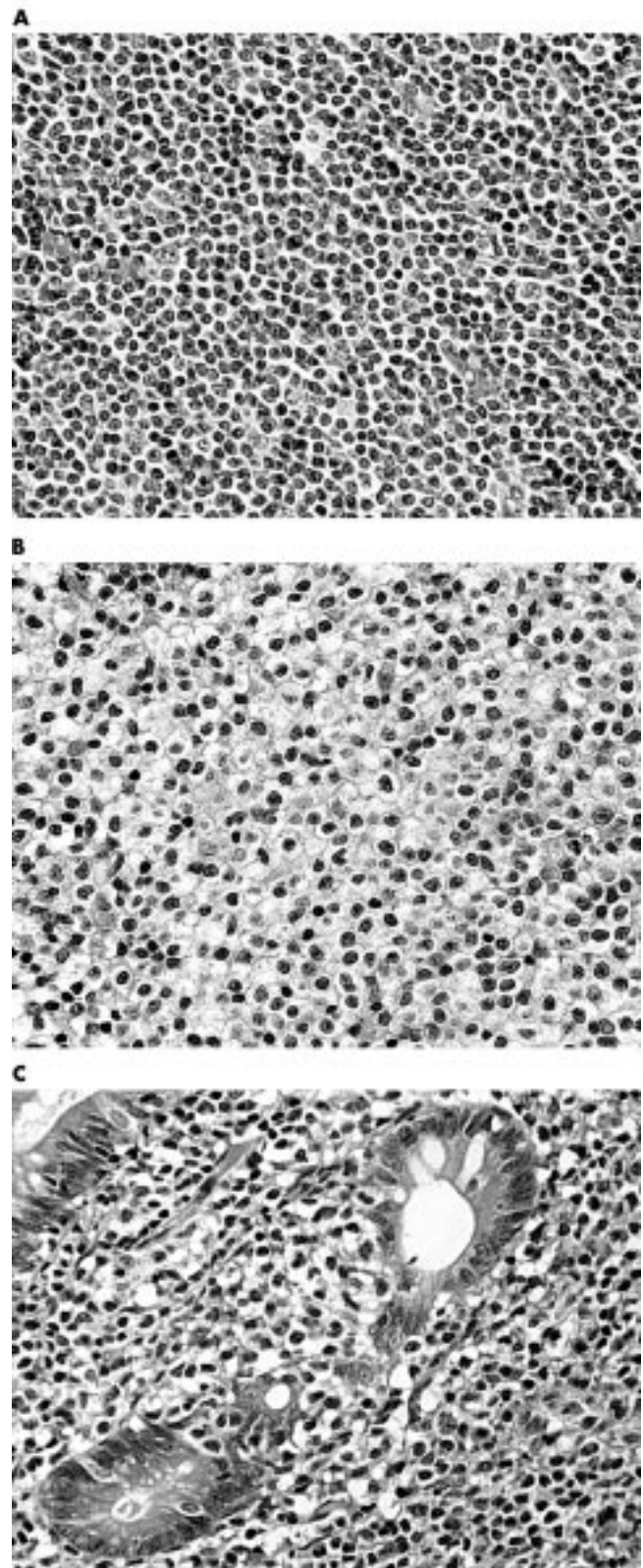


Figure 2 Histology of low grade mucosa associated lymphoid tissue (MALT) lymphoma. (A) A case of gastric MALT lymphoma positive for API2-MLT fusion transcripts (case 23). There is a diffuse proliferation of centrocyte-like cells resembling small lymphocytes in the gastric mucosa (haematoxylin and eosin stain; original magnification, ×600). (B) A case of gastric MALT lymphoma negative for API2-MLT fusion transcripts (case 5). A diffuse proliferation of centrocyte-like cells that have abundant clear cytoplasm resembling monocytoid B cells is seen (haematoxylin and eosin stain; original magnification, ×600). (C) A case of colonic MALT lymphoma positive for API2-MLT fusion transcripts (case 27). An infiltration of centrocyte-like cells forming a lymphoepithelial lesion can be seen in the colonic mucosa (haematoxylin and eosin stain; original magnification, ×600).

Table 1 Frequency of the API2–MLT fusion transcript in primary gastrointestinal lymphomas

Histological type	No. of patients	API2–MLT positive cases (%)
Low grade MALT lymphoma	28	4 (14)
Low grade MALT lymphoma with high grade component	4	0 (0)
Secondary DLBCL (high grade MALT lymphoma)	9	0 (0)
Primary DLBCL	4	0 (0)
T cell lymphoma	2	0 (0)

DLBCL, diffuse large B cell lymphoma; MALT, mucosa associated lymphoid tissue.

Aliquots of the cDNA solution (1 µl) were assayed by PCR for the API2–MLT chimaeric transcripts carrying the t(11;18)(q21;q21) translocation, using sense primer API2-S (5'-GCCCGCTTTAAAACATTCTTTAA-3') and antisense primer MLFAS (5'-GATTCCATTGCGCAATCCAG-3').²¹ Each reaction mixture (30 µl) contained 0.75 U AmpliTaq (Perkin Elmer, Foster City, California, USA), 10 mmol/litre Tris (pH 8.3 at 25°C), 1.5 mmol/litre MgCl₂, 0.2 mmol/litre of dNTP (Life Technologies), and 20 pmoles of each primer. The PCR reaction was carried out in a thermal cycler (Perkin Elmer) under the following conditions: 94°C for two minutes, followed by 35 cycles of denaturation for 20 seconds at 94°C, annealing for 20 seconds at 63°C, and extension for 30 seconds at 72°C. After the reaction, 10 µl aliquots of the PCR products were electrophoresed on a 1.6% agarose gel and stained with ethidium bromide. As a positive internal control, glyceraldehyde-3-phosphate dehydrogenase (GAPDH) was amplified, using the primer pair 5'-CGGGAACTGTGGCGTGATG-3' and 5'-AACTGTGAGGAGGGGAGATT-3'. The reaction conditions were: 94°C for five minutes, followed by 35 cycles of denaturation for one minute at 94°C, annealing for one minute at 58°C,

and extension for one minute at 72°C, with a final extension for seven minutes at 72°C.

Nucleotide sequence analysis

The amplified fragments were separated on agarose gel electrophoresis, purified, and 50 ng of each fragment was used for sequencing by the dideoxy chain termination method using an ABI PRISM BigDye terminator cycle sequencing ready reaction kit (Perkin Elmer). The nucleotide numbers were confirmed, according to the predicted amino acid number of API2 (GenBank accession number NM_001165) and MLT (GenBank accession number AF130356).

Conventional cytogenetic analysis

Fresh tissue specimens were obtained from 11 of the 47 patients. Conventional karyotypic analyses of the chromosomes of the cultured lymphoid cells were performed.²² Cell suspensions were obtained from the fresh specimens, and were cultured at 37°C for 24 hours in RPMI 1640 medium supplemented with 10% fetal calf serum, glutamine, and antibiotics. Metaphases were G banded by the GTG method. All karyotypes were described according to the international system for human cytogenetic nomenclature.²³

Statistical analysis

Statistical differences were evaluated by either Fisher's exact probability test or the χ^2 test. Probabilities of less than 0.05 were regarded as significant.

RESULTS

Frequency of the API2–MLT fusion transcript

The reference gene GAPDH was amplified by RT-PCR in all the cases. The API2–MLT fusion transcript was detected in four of 28 cases of low grade MALT lymphoma (figs 1, 2). The fusion transcript could not be detected by RT-PCR in the other types of lymphoma (table 1).

Table 2 Clinicopathological and molecular data of 28 patients with low grade MALT lymphoma

Patients	Age/sex	Origin	Macroscopic type	Depth of invasion	<i>Helicobacter pylori</i>	Treatment	Effect of <i>H pylori</i> eradication	Modified Ann Arbor stage	API2–MLT fusion
1	48/M	Stomach	Mass forming	mp	+	Erad	CR	II _{E1}	–
2	58/M	Stomach	Superficial	m	+	Erad	CR	IE ₁	–
3	59/F	Stomach	Superficial	m	+	Erad	CR	IE ₁	–
4	60/F	Stomach	Superficial	m	+	Erad	CR	IE ₁	–
5	66/F	Stomach	Superficial	m	+	Erad	CR	IE ₁	–
6	70/F	Stomach	Superficial	m	+	Erad	CR	II _{E1}	–
7	81/M	Stomach	Superficial	m	+	Erad	CR	IE ₁	–
8	64/M	Stomach	Superficial	m	+	Erad	CR	IE ₁	–
9	49/F	Stomach	Superficial	m	+	Erad	CR	IE ₁	–
10	65/M	Stomach	Superficial	m	+	Erad	CR	IE ₁	–
11	69/M	Stomach	Mass forming	m	+	Erad	CR*	IV	–
12	48/M	Stomach	Thick	mp	–	Erad	PR	IE ₂	–
13	65/F	Stomach	Superficial	m	+	Erad	PR	IE ₁	–
14	44/M	Stomach	Superficial	sm	+	Erad	NR	IE ₁	–
15	69/M	Stomach	Superficial	ss	+	Erad+Chemo	NR	II _{E1}	–
16	74/F	Stomach	Mass forming	mp	–	Erad+Chemo	NR	IE ₂	–
17	53/M	Stomach	Thick	sm	–	Erad+Rad	NR	IE ₁	+
18	54/F	Stomach	Superficial	m	+	Erad+Surg	NR	II _{E1}	–
19	47/M	Stomach	Superficial	m	+	Surg		IE ₁	–
20	54/F	Stomach	Superficial	m	+	Surg+Chemo		II _{E1}	–
21	66/M	Stomach	Superficial	m	+	Surg		IE ₁	–
22	72/F	Stomach	Thick	ss	+	Surg+Chemo		II _{E1}	–
23	41/F	Stomach	Superficial	sm	–	Surg+Chemo		II _{E1}	+
24	61/M	Stomach	Superficial	sm	–	Surg+Chemo		II _{E2}	–
25	48/F	Duodenum	Superficial	sm	+	Erad	PR	IE ₁	–
26	52/M	Colon	Mass forming	mp	–	Erad+Chemo	NR	IV	+
27	43/M	Colon	Thick	se	+	Erad+Surg	NR	IE ₂	+
28	54/M	Colon	Mass forming	sm	NA	Surg		IE ₁	–

Depth of invasion: m, mucosa; mp, muscularis propria; se, serosa; sm, submucosa; ss, subserosa. Treatment: Chemo, chemotherapy; Erad, *H pylori* eradication; Rad, radiation; Surg, surgery. Effect of eradication: CR, complete regression; PR, partial regression; NR, no regression. *Only the gastric lesion regressed completely in patient 11.
MALT, mucosal associated lymphoid tissue; NA, not available.

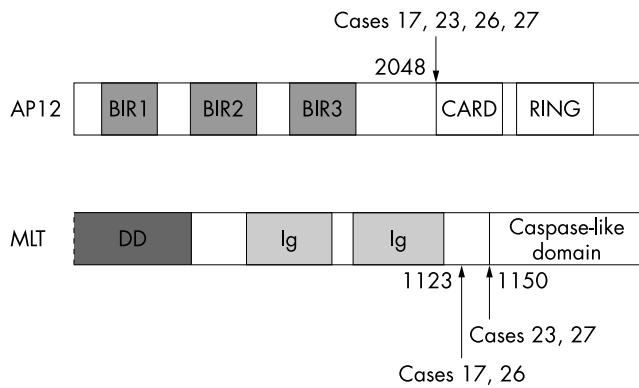


Figure 3 A schematic drawing of the breakpoints of the API2 and MLT genes in four cases positive for API2–MLT fusion transcripts. Numbering is in accordance with GenBank accession number NM_001165 for API2 and AF130356 for MLT. BIR, baculovirus IAP repeats; CARD, caspase recruitment domain; DD, death domain; Ig, immunoglobulin-like C2 domain; RING, zinc binding RING finger domain.

Table 2 shows the clinicopathological findings in relation to the results of analysis for the API2–MLT fusion transcript in the 28 cases of low grade MALT lymphoma. Of 24 gastric lymphomas, two patients were positive for the API2–MLT fusion transcript (patients 17 and 23). These tumours invaded the deep portion of the submucosa and there was no *H pylori*

infection. In contrast, the API2–MLT fusion transcript was detected in two of the three cases of low grade MALT lymphoma of the colon. One patient (patient 26) who was positive for the API2–MLT fusion transcript had a mass forming type tumour involving the muscularis propria of the transverse colon. The other patient (patient 27) had a diffuse infiltrating type tumour invading the serosa of the sigmoid colon with involvement of the stomach, the duodenum, the lungs, and the submandibular glands (stage IV).

Sequencing analysis of the API2–MLT fusion transcript

In the four cases positive for the API2–MLT fusion transcript, sequence analysis of the RT-PCR products identified a breakpoint for each gene. In these four cases, the breakpoint of the API2 gene was the same, at nucleotide 2048 of the gene. The breakpoint of the MLT gene varied and was seen at nucleotide 1123 or at 1150 (fig 3).

Conventional cytogenetic analysis

A conventional G banding analysis revealed that five of 11 lymphomas had abnormal karyotypes. Table 3 shows the histological types in relation to the abnormal karyotypes. t(11;18)(q21;q21) was found in two cases of colonic MALT lymphoma that were positive for the API2–MLT fusion transcript. These two cases had no other chromosomal abnormalities. Four other translocations were identified, namely: t(1;2)(p34;q21) and t(3;16)(p12;q12) in a case of low grade MALT lymphoma, t(6;11)(p23;q21) in a case of low grade

Table 3 Chromosomal translocations detected by G banding analysis

Histological type (case no.)	t(11;18)(q21;q21)	Other translocations
Low grade MALT lymphoma (13)	–	t(1;2)(p34;q21), t(3;16)(p12;q12)
Low grade MALT lymphoma (26)	+	–
Low grade MALT lymphoma (27)	+	–
Low grade MALT lymphoma with a high grade component	–	t(6;11)(p23;q21)
Secondary DLBCL	–	t(10;18)(q26;q11)

Case numbers in parentheses refer to the number indicated in table 2.
DLBCL; diffuse large B cell lymphoma; MALT, mucosal associated lymphoid tissue.

Table 4 Correlation between t(11;18)(q21;q21) positivity and clinicopathological factors in patients with low grade MALT lymphoma

Factors	API2–MLT positive cases (%)	API2–MLT negative cases (%)	p Value
Primary organ (n=28)			
Stomach	2 (8%)	22 (92%)	<0.05*
Duodenum	0 (0%)	1 (100%)	
Colon	2 (67%)	1 (33%)	
<i>Helicobacter pylori</i> status (n=27†)			
Positive	1 (5%)	20 (95%)	<0.05†
Negative	3 (50%)	3 (50%)	
Endoscopic appearance (n=28)			
Superficial	2 (10%)	18 (90%)	NS*
Mass forming	1 (25%)	3 (75%)	
Thick	1 (25%)	3 (75%)	
Clinical stage (n=28)			
IE ₁	1 (7%)	14 (93%)	NS*
IE ₂	1 (33%)	2 (67%)	
IIE or more	2 (20%)	8 (80%)	
Depth of invasion by EUS (n=28)			
Mucosa	0 (0%)	15 (100%)	<0.05†
Submucosa or beyond	4 (31%)	9 (69%)	
Response of <i>H pylori</i> eradication (gastric cases only; n=18)			
Complete or partial regression	0 (0%)	13 (100%)	NS†
No regression	1 (20%)	4 (80%)	

†Fisher's exact probability test; * χ^2 test; †one case was excluded because the *H pylori* status was not determined.

EUS, endoscopic ultrasonography; MALT, mucosal associated lymphoid tissue; NS, not significant.

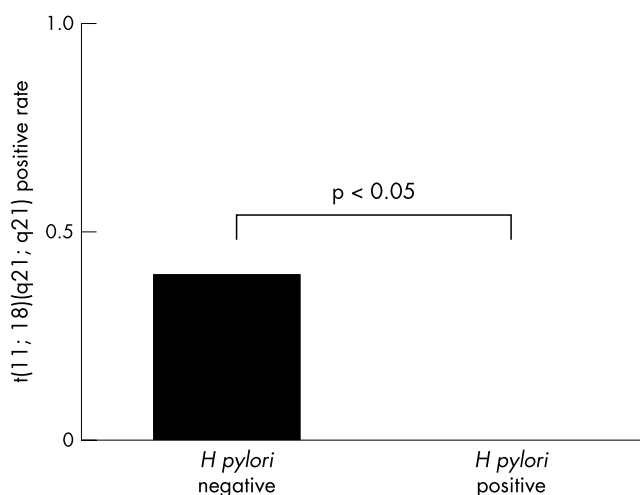


Figure 4 Comparison of the t(11;18)(q21;q21) positive rate in gastric MALT lymphoma according to *Helicobacter pylori* status. The fusion transcript was detected in 40% of *H. pylori* negative patients but in none of the 19 *H. pylori* positive patients.

MALT lymphoma with a focal high grade component, and t(10;18)(q26;q11) in a case of secondary DLBCL (table 3). The other six cases (four cases of low grade MALT lymphoma, a case of low grade MALT lymphoma with a focal high grade component, and a case of DLBCL) had no clonal chromosomal aberrations.

Correlation between the API2–MLT fusion transcript and the clinicopathological findings

Table 4 compares the clinicopathological findings of low grade MALT lymphoma between those positive and negative for the API2–MLT fusion transcripts. The API2–MLT fusion transcript was detected more frequently in MALT lymphoma of the colon (two of three) than in that of the stomach (two of 24) and the duodenum (none of one; $p < 0.05$), and in tumours that invaded the submucosa or beyond (four of 13) than in those restricted to the mucosa (none of 15; $p < 0.05$). The fusion transcript was detected more often in patients who were negative for *H. pylori* (three of six) than in those who were positive for *H. pylori* (one of 21; $p < 0.05$).

In gastric MALT lymphoma, the fusion transcript was detected in two of five *H. pylori* negative patients, whereas none of the 19 *H. pylori* positive patients harboured this translocation ($p < 0.05$) (fig 4). Among 18 patients with gastric low grade lymphoma treated for *H. pylori* eradication, 11 achieved a complete regression, two achieved partial regression, and five did not respond to *H. pylori* eradication. The only patient (patient 17) with gastric MALT lymphoma who was positive for the API2–MLT fusion transcript and *H. pylori* did not show regression after eradication. None of the patients who underwent complete or partial remission harboured the fusion transcript, whereas it was detected in one of the six patients who did not respond to treatment.

DISCUSSION

To date, the t(11;18)(q21;q21) translocation or the API2–MLT fusion transcript has been detected in approximately 20–30% of patients with extranodal low grade MALT lymphoma,^{5,6} but not in cases of DLBCL or high grade MALT lymphoma.²⁴ In our present study, this translocation was detected in four of 28 (14%) of the cases of low grade MALT lymphoma of the gastrointestinal tract, but not in other types of lymphoma (table 1). These results are comparable to those reported in previous investigations.^{5,6}

Our chromosomal G banding analysis confirmed the presence of t(11;18)(q21;q21) in two cases of low grade MALT lymphoma of the colon positive for the API2–MLT fusion

transcript, and this translocation was the sole chromosomal abnormality in these cases. There were only four other translocations, namely: t(1;2)(p34;q21) and t(3;16)(p12;q12) in a case of low grade MALT lymphoma, t(6;11)(p23;q21) in a case of low grade MALT lymphoma with a focal high grade component, and t(10;18)(q26;q11) in a case of secondary DLBCL. Ott *et al* reported that various types of chromosomal aberrations were found in 83% of high grade MALT lymphomas.⁶ The low frequency of translocations in our study is probably the result of the small sample size, especially in cases other than low grade MALT lymphoma.

In gastric low grade MALT lymphomas the reported frequency of t(11;18)(q21;q21) ranges from 0% to 48%. When we reviewed the data from 14 articles reported previously,^{5,6,10,11,24,26–34} this translocation was detected in 79 of 260 (30%) cases of gastric low grade MALT lymphoma. Liu *et al* detected this translocation frequently in MALT lymphomas of advanced stage.^{10,33} Recent publications have also reported that t(11;18)(q21;q21) is never seen in early gastric MALT lymphomas that regressed after *H. pylori* eradication treatment.^{10,11,29} As reported previously, our cases that showed regression after *H. pylori* eradication were negative for the API2–MLT fusion transcript (tables 2 and 4). Furthermore, the API2–MLT fusion transcript was detected more frequently in *H. pylori* negative patients than in those positive for *H. pylori*. Although our small sample size raises the possibility that the true incidence of the fusion transcript in *H. pylori* negative MALT lymphomas may be lower than that found in our present investigation, Nakamura *et al* also reported this translocation to be closely associated with *H. pylori* negative gastric MALT lymphoma.²⁵ These observations suggest that t(11;18)(q21;q21) may be related to the occurrence or progression of low grade MALT lymphoma in which *H. pylori* does not contribute to the pathogenesis.

As we found in our present investigation, others have reported that the clinical stage of gastric MALT lymphoma does not differ according to t(11;18)(q21;q21).^{10,21,26,30,31} The apparently insignificant contribution of t(11;18)(q21;q21) to the clinical stage seems to be partly explained by the low frequency of the translocation. However, two cases of gastric low grade MALT lymphoma positive for the translocation had invaded the submucosal layer. In addition, the frequency of the translocation was significantly higher in tumours with submucosal invasion than in those restricted to the mucosa when all the gastrointestinal MALT lymphomas were included for comparison. Even though the number of patients in our study was small, our findings are compatible with an observation by Liu and colleagues³³ that t(11;18)(q21;q21) is characteristic of advanced MALT lymphoma. Because the MALT lymphomas positive for t(11;18)(q21;q21) had no other chromosomal aberrations, it could be speculated that the translocation is associated with biologically aggressive MALT lymphoma.

“t(11;18)(q21;q21) may be related to the occurrence or progression of low grade mucosa associated lymphoid tissue lymphoma in which *H. pylori* does not contribute to the pathogenesis”

It is interesting to note that t(11;18)(q21;q21) was detected in two of the three colonic low grade MALT lymphomas. The two patients positive for the translocation had advanced tumours, which invaded the muscularis propria or serosa, whereas the patient who was negative had an early lymphoma restricted to the submucosa. To our knowledge, t(11;18)(q21;q21) has only been investigated in nine cases of colonic MALT lymphoma previously.^{26,27,30,31,35} As summarised in table 5, t(11;18)(q21;q21) was positive in eight of 12 cases of colonic MALT lymphoma. The positive rate seems to be higher than that observed in gastric MALT lymphomas.^{5,6,10,11,24,26–34} Although we found no differences between the

Table 5 Review of 12 reported cases of colonic MALT lymphoma positive for t(11;18)(q21;q21)

Reference	Age/ sex	Histological type	Stage	t(11;18)(q21;q21)	Breakpoint		Method for detection of t(11;18)(q21;q21)
					API2	MLT	
Motegi and colleagues ²⁶	45/M	Low with high	IIE	+	2048	1150	RT-PCR+G banding
Remstein and colleagues ²⁷	56/M	Low	IE	+	2048	814	RT-PCR+G banding
	ND	Low	ND	+	ND	ND	RT-PCR
Dierlamm and colleagues ³⁰	ND	Low	ND	-			RT-PCR
	ND	Low	ND	-			FISH+G banding
Inagaki and colleagues ³¹	60/M	Low	IIE	+	2048	541	RT-PCR
	62/F	Low	IE	-			RT-PCR
	66/M	Low	IIE	-			RT-PCR
Hosaka and colleagues ³⁵	56/F	Low	IE ₁	+			G banding
	Our case (no. 26)	52/M	Low	IV	+	2048	1123
Our case (no. 27)	43/M	Low	IE ₂	+	2048	1150	RT-PCR+G banding
Our case (no. 28)	54/M	Low	IE ₁	-			RT-PCR

Histological type: Low, low grade MALT lymphoma; Low with high, low grade MALT lymphoma with a focal high grade component. FISH, fluorescence in situ hybridisation; MALT, mucosa associated lymphoid tissue; ND, not described; RT-PCR, reverse transcription polymerase chain reaction.

t(11;18)(q21;q21) positive and negative patients with respect to the clinicopathological findings, it seems likely that this translocation may be more closely associated with the pathogenesis of colonic MALT lymphoma than with that of gastric MALT lymphoma. Recently, cases of colorectal MALT lymphoma that responded to *H pylori* eradication have been reported.³⁶⁻³⁸ Such rare cases may not be associated with t(11;18)(q21;q21); however, this speculation awaits future confirmation.

The breakpoints of the API2 and the MLT genes have been investigated previously in 58 cases of low grade MALT lymphoma positive for the API2-MLT fusion transcript, including our cases.^{10, 21, 25-27} The breakpoint of the API2 gene was at nucleotide 2048 in 35 of these 58 cases, whereas the breakpoint of the MLT gene varied. As shown in table 5, the breakpoint of the API2 gene was found at nucleotide 2048 in all five colonic cases, in contrast to that of the MLT gene, where the breakpoint was at nucleotides 541, 814, 1123, or 1150. Nucleotide 2048 of the API2 gene is located between the third BIR (baculovirus IAP repeats) domain and the C-terminal RING (zinc binding RING finger), and just upstream of the CARD (caspase recruitment domain). The BIR domains encode a function of apoptotic inhibition and the RING domain negatively regulates the antiapoptotic activity of them.³³ Stoffel *et al* reported that API2 mRNA was only expressed in mature B cells, whereas MLT mRNA was detectable in pre-B cells, in addition to mature B cells and plasma cells.³⁹ It can be speculated that aberrant expression of API2 might result in the deregulation of apoptosis in germinal centre B cells and the subsequent development of MALT lymphomas.

In conclusion, t(11;18)(q21;q21) is considered to be a characteristic chromosomal aberration in a certain proportion of gastrointestinal low grade MALT lymphomas, and to be one of the characteristic genetic alterations in this type of lymphoma. However, our results did not show a close association between the translocation and *H pylori* induced MALT lymphoma of the stomach. Although the number of subjects in our study was small, our results indicated that t(11;18)(q21;q21) may be closely associated with colonic MALT lymphoma, but not with gastric MALT lymphoma. Further investigations in a large number of patients is therefore warranted to clarify the role of this translocation in the pathogenesis of gastrointestinal MALT lymphomas.

ACKNOWLEDGEMENTS

The authors are grateful to Dr D Kang (Department of Clinical Chemistry and Laboratory Medicine, Graduate School of Medical Sciences, Kyushu University) for his technical assistance in sequencing

Take home messages

- The API2-MLT fusion transcript was seen in four of 28 cases of low grade mucosa associated lymphoid tissue (MALT) lymphoma, but not in other types of lymphoma
- The fusion transcript was seen more frequently in colonic tumours than in gastric tumours and was also more common in tumours with submucosal invasion than in those confined to the mucosa
- *Helicobacter pylori* negative tumours tended to have a higher positive rate than *H pylori* positive tumours
- None of the gastric tumours that responded to *H pylori* eradication expressed the API2-MLT fusion transcript
- Thus, the t(11;18)(q21;q21) translocation appears to be related to the development of gastrointestinal low grade MALT lymphoma but further investigations in a large number of patients are needed to clarify its role in the pathogenesis of gastrointestinal MALT lymphomas

analysis, and B Quinn for editing the manuscript. The content of this manuscript was presented in part at the 87th annual meeting of the Japanese Society of Gastroenterology, Tokyo, Japan (18 April 2001).

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