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ORIGINAL ARTICLE

Mucosa-associated lymphoid tissue lymphoma with t(11;18)(q21;q21) translocation: long-term follow-up results

Kosuke Toyoda[1] · Akiko Miyagi Maeshima[2] · Junko Nomoto[1,3] · Tomotaka Suzuki[1] · Sayako Yuda[1] · Nobuhiko Yamauchi[1] · Hirokazu Taniguchi[2] · Shinichi Makita[1] · Suguru Fukuhara[1] · Wataru Munakata[1] · Dai Maruyama[1] · Kensei Tobinai[1] · Yukio Kobayashi[1,3]

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Abstract

Translocation (11;18)(q21;q21) is found in mucosa-associated lymphoid tissue (MALT) lymphoma, resulting in API2/MALT1 gene fusion. It is known that t(11;18)-positive MALT lymphoma shows a tendency to disseminate and be resistant to *Helicobacter pylori* eradication by antibiotics. However, the prognostic features including recurrence and histological transformation (HT) remain unknown. We conducted a single-institute retrospective analysis of 464 patients with newly diagnosed MALT lymphoma, evaluating the impact of t(11;18) on clinical outcomes. One hundred and six patients were screened for the translocation by fluorescence in situ hybridization and/or reverse transcriptase-polymerase chain reaction. Of these patients, 26 patients (25%) were diagnosed as MALT lymphoma with t(11;18). The patients had a significantly shortened progression-free survival (PFS at 10 years; 26% *v* 57%; $P = 0.004$) compared to those without t(11;18). However, this did not translate into overall survival or incidence of HT. We confirmed previous reports stating that t(11;18)-positive MALT lymphoma showed disseminated disease and refractoriness to *H. pylori* eradication therapy. Patients with t(11;18) had more frequent monoclonal gammopathy, especially of IgM subtype (31% *v* 8%; $P = 0.008$), some of which developed class switch. These findings characterize the features of t(11;18)-positive MALT lymphoma, suggesting that it comprises a distinct clinical entity of MALT lymphoma.

Keywords MALT lymphoma · t(11;18)(q21;q21) · API2/MALT1 · Monoclonal gammopathy · Class switch

Introduction

Mucosa-associated lymphoid tissue (MALT) lymphoma, defined as extranodal marginal zone B cell lymphoma, accounts for 5–8% of non-Hodgkin lymphoma [1, 2]. The disease has a favorable prognosis; the 5-year overall survival (OS) probability of MALT lymphoma is higher than 90%, and the 10-year OS rate is 75–80% [1–3].

The t(11;18)(q21;q21) translocation is known as one of the most common genetic aberrations in MALT lymphoma (13–40%) [1, 2, 4, 5]. This chromosomal abnormality results in the juxtaposition of apoptosis inhibitor-2 (*API2*; also known as *c-IAP2* or *BIRC3*) with MALT translocation protein-1 (*MALT1*) gene [6–8]. It has been reported that API2/MALT1 protein activates both the canonical and non-canonical nuclear factor-kappa B (NF-κB) pathway [9–12]. Additionally, novel NF-κB-independent function of the protein was demonstrated as a gain-of-function oncogenic activity, resulting from cleavage of LIM domain and actin-binding protein 1 [13, 14].

t(11;18)-positive MALT lymphoma has been reported to originate mainly from the stomach and lung, with a propensity to disseminate. The gastric form is resistant to *Helicobacter pylori* eradication [1, 2, 15–17]. In addition to these clinical features, we previously reported that patients with t(11;18)-positive MALT lymphoma, confirmed by either fluorescence in situ hybridization (FISH) and/or reverse transcriptase-

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✉ Yukio Kobayashi
ykkobaya@iuhw.ac.jp

[1] Department of Hematology, National Cancer Center Hospital, Tokyo, Japan

[2] Department of Pathology, National Cancer Center Hospital, Tokyo, Japan

[3] Department of Hematology, International University of Health and Welfare, Mita Hospital, 1-4-3 Mita, Minato-ku, Tokyo 108-8329, Japan

polymerase chain reaction (RT-PCR), were also associated with monoclonal gammopathy [18]. However, information on prognosis and frequency of histological transformation (HT) in a long-term follow-up is limited. Herein, we provide an update to our previous study [19] with a longer observation period, and we have tried to elucidate the clinical impact of this genetic aberration on the prognosis of MALT lymphoma, comparing patients with t(11;18)(q21;q21) translocation with those without.

Methods

Patient selection

Archives of patients with MALT lymphoma diagnosed between 1997 and 2014 at the National Cancer Center Hospital, Tokyo, Japan, were used after confirmation of informed consent. The cohort consisted of 467 patients in our previous study. From this cohort, we carefully omitted duplicated cases that were counted twice or more due to multiorgan tumor sites. In this study, information on the presence or absence of t(11;18) was added. In addition to the archive data, we also added patients referred to our institute requesting examination of the translocation. Cases were categorized by detection of the translocation: positive and negative.

We collected clinical data, such as age, sex, primary site of lesion, number of extranodal lesions, Ann Arbor stage, International Prognostic Index (IPI), therapy, outcome, and presence of HT, monoclonal gammopathy, and t(11;18). Monoclonal gammopathy was judged to be positive if electrophoresis had M-bow, and if gammopathy existed, the IgA, M, and G level was measured and confirmed by immunoelectrophoresis. Gastrointestinal lymphoma was staged according to the Lugano staging system of gastrointestinal tract lymphoma [20]. Patients who had only a single lesion of the lung were categorized as stage I with modification, consistent with our previous study [19].

Response to therapy was assessed based on standard response criteria [21]. HT was diagnosed by two hematopathologists according to the following criteria: large lymphoma cells accounting for more than 30% of the specimen with coexistence of small and large lymphoma cells, or monotonous proliferation of large lymphoma cells; the cutoff level was defined in our previous report [19]. After diagnosis of HT, these patients were divided into two groups, "synchronous" or "asynchronous," in accordance with the timing of HT occurrence [19].

To investigate incidence of dissemination in t(11;18)-positive MALT lymphoma, we defined disseminated disease as Ann Arbor stage III to IV in non-gastrointestinal MALT lymphoma, Lugano stage I with multiple gastrointestinal lesions, or Lugano stage IV. Remaining patients were classified as having localized disease.

The present study was granted ethical approval by the institutional review board of the National Cancer Center (2016-278) and was conducted in compliance with the Declaration of Helsinki.

Detection of the t(11;18)(q21;q21) translocation

Selection of patients to determine the presence or absence of t(11;18) by FISH and/or RT-PCR was arbitrary, but when the patients were noticed to have elevated levels of IgM, the patients were likely to be examined. In the FISH analysis, we used a "Histology FISH Accessory Kit" (Dako, Glostrup, Denmark) with an API2/MALT1 dual color, dual fusion DNA probe, which hybridizes to chromosome 11q21 and chromosome 18q21 (Vysis, Inc., Downers Grove, IL) as previously reported [18]. RT-PCR assay was performed with a one-tube RT-PCR system and PCR core kit (Roche Diagnostics K.K., Tokyo, Japan) according to published data [6].

IgM and IgG of each patient were measured, and when either level was elevated, and t(11;18) was shown, we examined *MYD88* gene status to rule out Waldenström macroglobulinemia (WM). We detected the *MYD88* gene mutation using allele-specific PCR and Sanger sequencing, based on previous publications [22].

Statistical analysis

Patient characteristics were analyzed using Fisher's exact test, χ^2 test (for primary site of lesion and initial therapy) and the Mann-Whitney *U* test (for age).

MALT-IPI, a prognostic index for MALT lymphomas, was recently proposed [23]. We performed further analyses including survival, according to the index in patients whose MALT-IPI scores were calculable.

The probability of survival was estimated by the Kaplan-Meier method and compared using the log-rank test statistics. Progression-free survival (PFS) was measured from the date of initial diagnosis to either the first documentation of objective disease progression, or to the date of death as a result of any cause. OS was measured from the date of initial diagnosis to the date of death by any cause. The cumulative incidence by Gray test was performed to assess a frequency of HT. Parameters were the presence of t(11;18), number of extranodal lesions (≥ 2), disseminated disease, the occurrence of HT, age, and gastrointestinal or not. Univariate analysis was performed using Cox regression analysis. All statistical analyses were determined significant for *P* values less than 0.05 and performed with EZR ver.3.3.3 [24]. We conducted multivariate Cox proportional hazards regression analysis to detect variables affecting PFS. In the multivariate analysis, factors whose *P* value was less than 0.10 were used as a result of univariate analysis.

Results

Patient characteristics

The previous cohort consisted of 467 patients [19], from which we omitted 16 duplicated cases, before adding 13 new cases referred to our institution requesting testing for the translocation. A total of 464 patients were subject to analyses. The patient characteristics are listed in Table 1. Among them, 106 patients had been examined for t(11;18). Of these patients, 26 (25%) were categorized as positive for t(11;18), whereas 80 patients were negative following examination.

The main clinical features of patients with MALT lymphoma with t(11;18) are summarized in Table 2. We found 10 patients with multiple involvement. Triplicated origins were found in five; these patients had combined lesions of the stomach, lung, and intestine; stomach, lung, and pleura; stomach, bone marrow (BM), and peripheral blood (PB); lung, pleural effusion, and BM; and orbit, BM, PB, and lymph nodes. Duplicated origins existed in five patients: three originating in the stomach and lung and two in the stomach and intestine. In the remaining 16 patients, the primary site was solitary; six patients showed origin in the stomach, six in the lung, two in the intestine, one in orbit, and one in salivary gland.

The incidence of t(11;18) was 56% in MALT lymphomas with multiple involvement, 30% in pulmonary MALT lymphomas, 24% in the stomach, and 5% in ocular MALT lymphomas. Out of 26 patients with t(11;18), 20 (77%) had been diagnosed by the routine medical checkup system such as upper gastrointestinal endoscopy and chest X-ray. As listed in Table 2, the other six patients were identified by presentation of lymphoma-related symptoms; two patients of ocular MALT lymphoma by tumor of the ocular adnexal mass, two patients by respiratory symptoms such as cough, a salivary gland patient by topical mass, and a gastric patient by abdominal symptoms including gastric ulcer and bleeding.

MALT-IPIs are shown in Table 1. Of our patients with t(11;18), five, seven, and four patients belonged to low, intermediate, and high index groups, respectively. Of our patients without t(11;18), 32, 33, and 8 were categorized in the low, intermediate, and high index groups, respectively. The remaining 10 (38%) patients in the positive group and seven (9%) in the negative group were not assessed for MALT-IPI, mainly because of a lack of serum lactate dehydrogenase data (Table 1).

Seven patients among 19 examined patients had monoclonal gammopathy at manifestation, accounting for 37% of t(11;18)-positive patients. Six patients had an elevated level of IgM, range 1458–8884 mg/dL, and one had monoclonal IgG of 2670 mg/dL at manifestation (Table 2). Of the six patients with IgM paraprotein, two underwent class switch; one from IgM to IgA and the other from IgM to IgG at 3.5 and 7 years, respectively. An elevated level of IgM gradually decreased and normalized with the emergence of the second monoclonal protein. Among the remaining 12 patients, one had no monoclonal gammopathies observed at manifestation, but the patient was found to have biclonal IgM and IgG paraprotein; the patient showed IgG and IgM levels of 2589 mg/dL, and 352 mg/dL, after 204 months from the initial 1302 mg/dL and 109 mg/dL, respectively.

Comparison of patients with t(11;18) and those without was also made. Patients with t(11;18)-positive MALT lymphoma had more extranodal lesions (≥ 2; 39% *v* 16%; $P = 0.027$). Primary sites, defined as the largest mass, of t(11;18)-positive MALT lymphoma with multiple involvement, were mainly the lung and stomach, accounting for 90%, as previously reported [1, 2, 17].

Treatment result, survival analysis, and incidence of HT

As listed in Tables 1 and 2, the initial therapies of 26 patients with t(11;18) were heterogeneous. Treatments included *H. pylori* eradication in seven, surgery in six, watchful wait (W/W) in six, R-CHOP ± radiotherapy in five, radiotherapy in three, and CHOP ± radiotherapy in two.

Treatment effects in t(11;18)-positive MALT lymphoma were evaluated in 20 patients, excluding six W/W patients. Nine of 20 (45%) achieved complete response (CR), two (10%) partial response (PR), seven (35%) stable disease, and two (10%) progressive disease (Table 2). Thus, 11 of 20 patients who received anti-lymphoma treatment did not achieve CR, accounting for 55%. Of these 11 non-CR patients, 10 (91%) eventually experienced relapse or disease progression with a median time of 18.5 months from their diagnosis. Among the six W/W patients with no intervention being made, five (83%) progressed with a median time of 30 months after their diagnosis. Only one patient maintained stable disease under W/W.

The treatment was partially dependent on the site of the tumor, and its effect was also dependent on the treatment. We found that t(11;18)-positive MALT lymphoma in the stomach was refractory to *H. pylori* eradication therapy; seven of eight (88%) patients with t(11;18) were resistant to this treatment and only one patient achieved CR.

The median follow-up period was 120 months, ranging 9 days to 337 months ($n = 106$). The rate of OS at 10 years was 91% (95% confidence interval [CI], 81–95). Survival according to the presence or absence of t(11;18) is shown in Fig. 1. OS among each group was similar without statistical difference (Fig. 1a; positive *v* negative, 87% [95% CI, 58–97] *v* 92% [95% CI, 81–96], respectively; $P = 0.58$); the hazard ratio (HR) was 0.65 (95% CI, 0.14–3.06).

As shown in Fig. 1b, PFS was significantly different when compared among patients with the translocation and those without; the probability of PFS at 10 years was 26% (95%

Table 1 Clinical and demographic characteristics at baseline

	Total (N = 464)		Positive (n = 26)		Negative (n = 80)		P^d
	N	%	n	%	n	%	
Sex							0.012
Male	233	(50)	20	(77)	38	(48)	
Female	231	(50)	6	(23)	42	(53)	
Age							0.051
Median, years (range)	61	(12–89)	55	(29–79)	61	(12–85)	
IPI							0.414
Low/Low-intermediate	252	(54)	9	(35)	50	(63)	
High-intermediate/High	21	(5)	3	(12)	9	(11)	
NA	191	(41)	14	(54)	21	(26)	
MALT-IPI							0.325
Low	192	(41)	5	(19)	32	(40)	
Intermediate	156	(34)	7	(27)	33	(41)	
High	46	(10)	4	(15)	8	(10)	
NA	70	(15)	10	(38)	7	(9)	
Ann Arbor stage							0.075
I/II	407	(88)	15	(58)	62	(78)	
III/IV	57	(12)	11	(42)	18	(23)	
Lugano stage							1.0
I to IIE	218		10		21		
I (multiple gastrointestinal lesions)	4		2		0		
IV	8		0		2		
Dissemination							0.075
Localized disease	407	(88)	15	(58)	62	(78)	
Disseminated disease	57	(12)	11	(42)	18	(23)	
Number of extranodal lesions							0.027
1	424	(91)	16	(62)	67	(84)	
≥ 2	40	(9)	10	(38)	13	(16)	
Primary site of lesion							0.029
Multiple	31	(7)	10	(38)	8	(10)	
Stomach	204	(44)	6	(23)	19	(24)	
Lung	37	(8)	6	(23)	14	(18)	
Conjunctiva	64	(14)	0	(0)	10	(13)	
Orbit	53	(11)	1	(4)	9	(11)	
Salivary glands	17	(4)	1	(4)	7	(9)	
Thyroid	16	(3)	0	(0)	1	(1)	
Intestine	17	(4)	2	(8)	3	(4)	
Skin	9	(2)	0	(0)	6	(8)	
Others[a]	16	(3)	0	(0)	3	(4)	
Monoclonal gammopathy							0.008
IgM	13	(3)	6[b]	(23)	4	(5)	
IgM and IgG	1	(0)	1	(4)	0	(0)	
IgG	5	(1)	1	(4)	2	(3)	
None	269	(58)	11	(42)	48	(60)	
NA	176	(38)	7	(27)	26	(33)	
Histologic transformation							1.0
Synchronous	29	(6)	1	(4)	4	(5)	

Table 1 (continued)

	Total (N = 464)		Positive (n = 26)		Negative (n = 80)		P^d
	N	%	n	%	n	%	
Asynchronous	13	(3)	0	(0)	2	(3)	
None	422	(91)	25	(96)	74	(93)	
Initial therapy							0.137
H. pylori eradication	179	(39)	7	(27)	18	(23)	
RT	112	(24)	3	(12)	22	(28)	
W/W	93	(20)	6	(23)	24	(30)	
R-CHOP±RT[c]	35	(8)	5	(19)	6	(8)	
CHOP±RT[c]	22	(5)	2	(8)	5	(6)	
Surgery	14	(3)	3	(12)	2	(3)	
R monotherapy	9	(2)	0	(0)	3	(4)	

IPI international prognostic index, *NA* not applicable, *MALT* mucosa-associated lymphoid tissue, *H. pylori helicobacter pylori*, *RT* radiotherapy, *W/W* watchful wait, *R* rituximab, *CHOP* cyclophosphamide, doxorubicin, vincristine, and prednisone, *CVP* cyclophosphamide, vincristine, and prednisone

[a] Includes breast (5), thymus (4), urinary bladder (2), bronchus (1), esophagus (1), nasal cavity (1), vertebral bone (1), and vocal cord (1) lesions in total patients, and thymus (2) and bronchus (1) in negative group

[b] Includes two patients with class switch

[c] CHOP includes modified therapies such as CVP regimen

[d] *P* value between positive and negative group

confidence interval [CI], 10–45) in the t(11;18)-positive group, compared with 57% (95% CI, 44–68) in the negative group ($P = 0.004$; HR, 2.31 [95% CI, 1.29–4.11]). The result was unrelated to the extent of dissemination; the probability of PFS at 10 years in patients with t(11;18) was significantly shorter in both localized and disseminated disease when compared with those without the translocation in each group. In localized disease, t(11;18)-positive MALT lymphoma showed a trend of lower probability of PFS at 10 years, although no significant difference was shown (Fig. 1c; 19% *v* 57%; $P = 0.071$; HR, 1.96 [95% CI, 0.93–4.12]). In disseminated disease, t(11;18)-positive MALT lymphoma showed significantly shorter PFS at 10 years with a statistically significant difference (Fig. 1d; 32% *v* 58%; $P = 0.036$; HR, 2.89 [95% CI, 1.02–8.16]).

We could not find any difference in the incidence of HT between t(11;18)-positive and negative groups (Fig. 2; 15-year cumulative incidence of HT, 4% *v* 8%; $P = 0.497$; HR, 0.49 [95% CI, 0.06–4.09]). Of 26 patients with t(11;18), one patient was found to have HT at diagnosis. This patient was found to have MALT lymphoma in the stomach, PB, and BM. Both the PB tumor cells and the stomach lesion had t(11;18), detected by FISH analysis, which confirmed they originated from the same clone. The gastric lesion biopsied from multiple sites by endoscopy showed either MALT lymphoma or diffuse large B cell lymphoma (DLBCL); therefore, the patient was diagnosed as having synchronous HT. Indeed, they showed a composite nature of the lymphoma, MALT lymphoma, and DLBCL, which is suggestive of progressive transformation of MALT lymphoma. In both area, the t(11;18) was demonstrated. The patient also showed monoclonal IgM paraprotein and disseminated disease. Despite this HT with t(11;18) at presentation and later relapse, the patient was alive at the time of preparation of this manuscript (patient no. 4 in Table 2).

We performed a multivariate analysis for PFS using the following parameters: the presence of t(11;18), number of extranodal lesions (≥ 2), disseminated disease, the occurrence of HT, age, and gastrointestinal or not. Table 3 summarizes the results of the regression model analysis among the patients with known t(11;18) status. The multivariate analysis also demonstrated that the presence of t(11;18) significantly influences PFS ($P = 0.033$; HR, 1.93 [95% CI, 1.06–3.55]).

Validation of the MALT-IPI

The MALT-IPI was calculable in 394 patients of our entire cohort, consisting of 192 in the low risk, 156 in the intermediate risk, and 46 in the high risk (Table 1). The rates of OS at 10 years were 98% (95% CI, 93–99), 97% (95% CI, 91–99), and 74% (95% CI, 54–87) as shown in Fig. 3a (log-rank test; $P < 0.001$), whereas those of PFS at 10 years were 80% (95% CI, 72–86) in the low risk, 77% (95% CI, 69–84) in the intermediate risk, and 63% (95% CI, 44–77) in the high risk, respectively (Fig. 3b; log-rank test; $P = 0.035$).

Table 2 Main clinical features of 26 patients with MALT lymphoma carrying t(11;18)(q21;q21) translocation

Patient no.	Age	Sex	Primary site of lesion	Detected by routine medical check up system	Ann Arbor stage	Lugano stage	Initial therapy	Response to initial therapy	Resistance to *H. pylori* eradication [b]
1	79	M	Intestine	Yes	II	II_1	W/W	–	–
2	40	F	Lung	Yes	I	–	CHOP	SD	–
3	34	M	Lung (multiple)	Yes	IV	–	W/W	–	–
4	37	M	Multiple (stomach/BM/PB)	No (cough)	IV	–	R-CVP	SD	–
5	56	F	Multiple (stomach/lung/pleura)	Yes	IV	–	R-CHOP [a]	PR	–
6	63	M	Multiple (stomach/intestine)	Yes	IV	I (multiple)	*H. pylori* eradication	SD	Yes
7	61	M	Multiple (stomach/lung/intestine)	Yes	IV	–	W/W	–	–
8	53	M	Orbit	No (tumor enlargement)	I	–	RT	CR	–
9	67	M	Multiple (stomach/lung)	Yes	IV	–	W/W	–	–
10	60	M	Stomach	No (bleeding stomach ulcer)	I	I	*H. pylori* eradication	PD	Yes
11	36	M	Stomach	Yes	II	II_1	R-CHOP+RT	CR	–
12	58	M	Stomach	Yes	I	I	*H. pylori* eradication	CR	No
13	55	M	Multiple (orbit/BM/PB/LNs)	No (tumor enlargement)	IV	–	R-CHOP	PR	–
14	44	F	Multiple (stomach/lung)	Yes	IV	–	Excision followed by RT	CR	–
15	29	M	Multiple (stomach/lung)	Yes	IV	–	R-CHOP	CR	–
16	62	M	Multiple (stomach/intestine)	Yes	IV	I (multiple)	*H. pylori* eradication	SD	Yes
17	61	F	Lung	Yes	I	–	W/W	–	–
18	48	M	Stomach	Yes	I	I	*H. pylori* eradication	SD	Yes
19	55	M	Stomach	Yes	I	I	*H. pylori* eradication	SD	Yes
20	55	M	Lung	Yes	I	–	W/W	–	–
21	52	M	Salivary gland	No (tumor enlargement)	I	–	RT	CR	–
22	68	M	Intestine	Yes	I	I	Surgery	CR	Yes
23	68	M	Lung	Yes	I	–	Surgery	CR	–
24	55	F	Lung	Yes	I	–	Surgery	CR	–
25	60	F	Stomach	Yes	I	I	*H. pylori* eradication	SD	Yes
26	53	M	Multiple (lung/pleural effusion/BM)	No (cough)	IV	–	CHOP	PD	NA

Patient no.	Time to 1st progression from diagnosis (months)	MALT-IPI	2nd line therapy ‡	Histologic transformation	Monoclonal gammopathy	Maximum of IgM (mg/dL)	Outcome
1	30	High	R monotherapy	No	IgM	3937	Dead (colorectal cancer)
2	68	NA	Oral etoposide	No	IgM switched to IgA	5360	Alive
3	90	NA	CHOP	No	IgM	1864	Alive
4	27	Intermediate	R monotherapy	Synchronous	IgM switched to IgG	8884	Alive
5	13+	Intermediate	–	No	IgM	3085	Alive
6	6	Intermediate	RT and excision	No	IgM	1458	Alive
7	136	High	R-CHOP	No	None to both IgM and IgG	352	Alive
8	76	NA	RT	No	IgG	2670 (IgG)	Alive
9	9	Intermediate	R monotherapy	No	None	178	Alive
10	6	Low	RT	No	None	61	Alive

Table 2 (continued)

11	84+	Low	–	No	None	137	Dead (gastric cancer)
12	50+	Low	–	No	None	127	Alive
13	41	High	Obinutuzumab	No	None	29	Alive
14	114+	Intermediate	–	No	None	194	Alive
15	129	High	W/W	No	None	76	Alive
16	13	NA	C-MOPP	No	None	126	Alive
17	305+	NA	–	No	None	89	Alive
18	238	Intermediate	W/W	No	None	75	Alive
19	5	NA	RT	No	None	90	Alive
20	25	NA	W/W	No	NA	91	Alive
21	34	NA	W/W	No	NA	83	Alive
22	82	NA	*H. pylori* eradication	No	NA	113	Alive
23	75+	Low	–	No	NA	74	Alive
24	77	Intermediate	W/W	No	NA	244	Alive
25	24	Low	NA	No	NA	NA	NA
26	8	NA	NA	No	NA	NA	NA

MALT, mucosa-associated lymphoid tissue; *M*, male; *F*, female; *BM*, bone marrow; *PB*, peripheral blood; *LNs*, lymph nodes; *NA*, not applicable; *W/W*, watchful wait; *CHOP*, cyclophosphamide, doxorubicin, vincristine, and prednisone; *R*, rituximab; *CVP*, cyclophosphamide, vincristine, and prednisone; *RT*, radiotherapy; *H. pylori*, *Helicobacter pylori*; *SD*, stable disease; *PR*, partial response; *CR*, complete response; *PD*, progressive disease; *IPI*, international prognostic index; *C-MOPP*, cyclophosphamide, vincristine, procarbazine, and prednisone. [a] Followed by R maintenance therapy. [b] "-" means a patient who was not treated with eradication of *H. pylori*

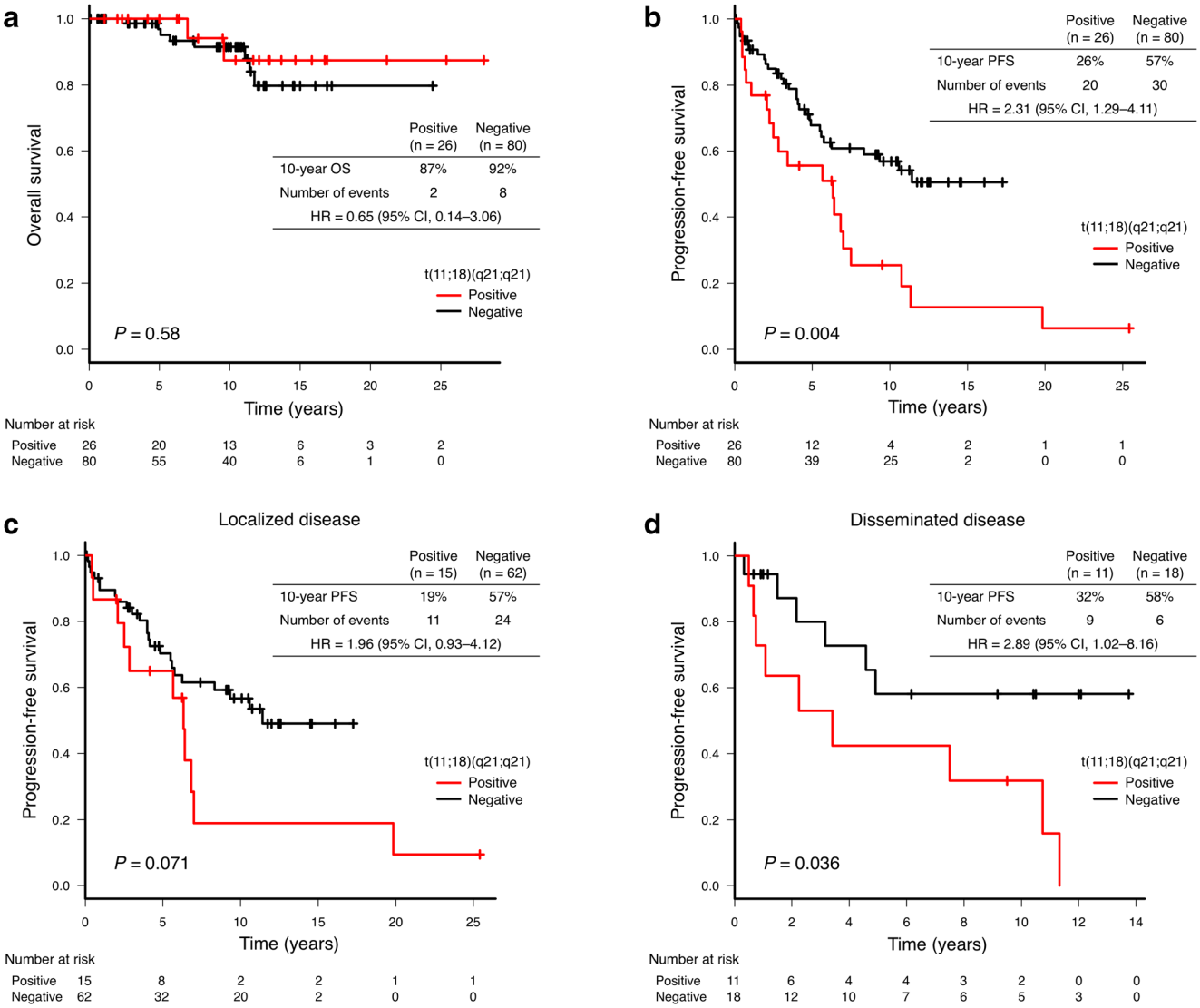

Fig. 1 Survival curves of the patients tested for t(11;18)(q21;q21) translocation, comparing t(11;18)-positive group with negative group ($n = 106$). **a** Overall survival (OS) and **b** progression-free survival (PFS) categorized with or without t(11;18). **c** Localized disease and **d** disseminated disease, in which PFS curves classified by dissemination were compared by the presence or absence of t(11;18); HR, hazard ratio; CI, confidence interval

Discussion

We found 26 patients presenting with t(11;18) MALT lymphoma among 106 patients tested for the translocation. The incidence was 25% and was comparable to that of previous reports [1, 15, 25, 26]. The incidence of the translocation among MALT lymphoma differs according to tumor site and has been previously reported [5, 15]. Streubel et al. reported that occurrence is the highest in the lung (53%), followed by gastric (24%), and ocular (3%) sites [5]. Liu et al. also reported the lung (57%) and stomach (34%) as sites of highest incidence, albeit with differing frequency [15]. The distribution of the t(11;18) was also confirmed by the present analysis; among our cohort of MALT lymphoma with t(11;18), the most common primary site was the lung followed by the stomach.

The comparison of patients with and without t(11;18) showed that the number of extranodal lesions was greater and monoclonal gammopathy was more frequent, the character of which we already know. This analysis confirms that MALT lymphoma with t(11;18) shows disseminated and frequent monoclonal gammopathy.

To the best of our knowledge, this is the first report to analyze the impact of API2/MALT1 fusion on prognosis including PFS, OS, and the incidence of HT. We found a higher recurrence rate in MALT lymphoma involving t(11;18) with significantly shorter PFS at 10 years than in patients without the translocation; PFS of patients with t(11;18)-positive MALT lymphoma was 26%, whereas that of those without the translocation was 57% ($P = 0.004$). This contrasts with the previous report by Raderer et al., which found that patients

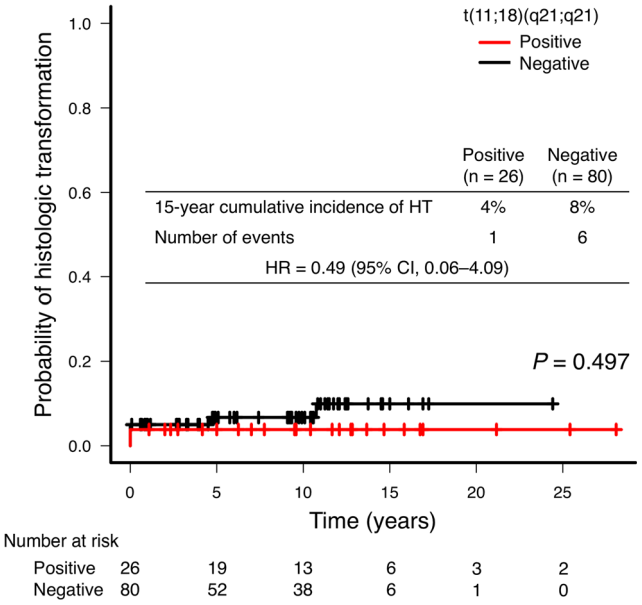

Fig. 2 Cumulative incidence of histological transformation (HT) according to the presence or absence of t(11;18)(q21;q21) translocation ($n = 106$)

with t(11;18)-positive MALT lymphoma showed longer median time to relapse than those without the translocation. In their report, the median time to relapse was 76 months in the patients with t(11;18), compared with 29 months in those lacking the translocation ($P = 0.012$) [26].

The discrepancies between these two studies might be explained by the different characteristics of the cohorts. Raderer et al. analyzed only those patients who achieved CR after initial therapy including chemotherapy, radiotherapy, excision, and *H. pylori* eradication therapy. Thus, they did not include either primary refractory or non-CR patients after initial treatment. Because we analyzed all the patients with t(11;18), we may have included cases of more aggressive disease. To test this hypothesis, the prognosis of 11 patients with t(11;18) who did not achieve CR by initial therapies was analyzed. Ten patients (91%) experienced relapse or disease progression. The median time to relapse or progression from diagnosis of these patients was 18.5 months, which is markedly shorter than that in Raderer's report. These findings suggest that the difference might be partly derived from inclusion of non-CR patients in our study.

The prognosis can be influenced by the treatment modality, which depends on the primary site. To assess the impact of primary site, we included the primary site as a variable in the analysis and found that the impact disappears in the multivariate analysis; rather, only the presence of t(11;18) and number of extranodal lesions significantly influenced on PFS.

This is the first report to analyze the OS at 10 years in patients with MALT lymphoma with t(11;18). The shorter PFS of those patients was not translated to shorter OS; of 26 patients with t(11;18) whose survival was analyzed, two patients expired due to colorectal cancer and gastric cancer without lymphoma; however, the remaining patients survived. The 10-year OS of patients with t(11;18) was 87%, and that of patients lacking the translocation was 92%. The OS data of MALT lymphoma obtained from the surveillance, epidemiology, and end results (SEER) database showed that 10-year OS of MALT lymphoma was 58% [27]. We cannot precisely know the reasons for this discrepancy, but it may be attributable to the differences in methods of examination by which we identified disease. Twenty (77%) of 26 patients with t(11;18) had been diagnosed through the annual routine medical checkup system in our series, which is a common practice in our country [28]. These patients might have been found later at a more advanced stage if they had not participated in the routine medical checkup system. To support this hypothesis, the median age of patients with the translocation was 55 years, ranging from 29 to 79, and median age of the SEER data was 67 years, ranging from 55 to 77.

Recently, MALT-IPI was proposed using data obtained from a clinical trial [23]. To our knowledge, this is the first validation study of the index. First, we compared the PFS in the subset in which MALT-IPI was available; in approximately 60% of patients, lactate dehydrogenase data were obtained and MALT-IPIs were successfully calculated. In this subset, PFS in patients with t(11;18) was again significantly worse compared with those without the translocation (log-rank test; $P = 0.022$, Supplementary Fig. 1). However, the MALT-IPI did not have a significant effect on PFS in this subset ($P = 0.181$, Supplementary Fig. 2), which suggested that the presence or absence of the translocation affects more than the MALT-IPI.

Our entire cohort was large enough to validate the index. The distribution of our patients was comparable to the previous report, where 167, 165, and 68 patients were low, intermediate, and high, respectively. By using the index, PFS and OS in our study were also statistically different. Even though the current study was retrospectively conducted, our findings could confirm its clinical usefulness.

It has been recognized that HT occurs in MALT lymphoma with a probability of 3–12% [19, 29, 30]. This is the first study to examine the incidence of HT in MALT lymphoma with t(11;18); only one patient with t(11;18) had synchronous HT, and despite this, the patient survived. Other MALT lymphoma patients with the translocation also survived until the last follow-up. Our cohorts are still too small, and whether patients with t(11;18) have the tendency not to develop HT remains to be found.

The present study demonstrated a high frequency of monoclonal gammopathy, particularly of IgM type, in patients with t(11;18). High levels of IgM are not limited to cases with WM/lymphoplasmacytic lymphoma (LpL) [31]. WM/LpL is the most common malignancy demonstrating high levels of IgM so *MYD88* L265P was examined and WM/LpL was ruled out

Table 3 Univariate and multivariate analysis of clinical parameters influencing progression-free survival, among the patients tested for t(11;18)(q21;q21) translocation ($n = 106$)

Variable		Univariate			Multivariate		
		HR	95% CI	*P*	HR	95% CI	*P*
Presence of t(11;18)							
No	($n = 80$)	1	1.29–4.11	0.005	1	1.06–3.55	0.033
Yes	($n = 26$)	2.31			1.93		
Number of extranodal lesions							
1	($n = 83$)	1	1.33–4.59		1	1.06–3.86	
≥2	($n = 23$)	2.48		0.004	2.02		0.033
Dissemination							
Localized disease	($n = 77$)	1	0.76–2.56				
Disseminated disease	($n = 29$)	1.39		0.289			
Histologic transformation							
No	($n = 99$)	1	0.54–4.18				
Yes	($n = 7$)	1.50		0.436			
Age > 70							
No	($n = 89$)	1	0.65–2.78				
Yes	($n = 17$)	1.35		0.423			
Primary site of lesion							
Non-GI tract	($n = 74$)	1					
GI tract[a]	($n = 32$)	1.62	0.89–2.96	0.114			

GI, gastrointestinal; *HR*, hazard ratio; *CI*, confidence interval

[a] Incudes Lugano stage I with multiple gastrointestinal lesions

in our patients [22, 32]. These findings confirm that MALT lymphoma involving t(11;18) has a tendency to be associated with monoclonal gammopathy, updating the data from our previous cohort included in this study [18]. In fact, there are multiple case reports that demonstrate the relationship between the presence of t(11;18) and monoclonal gammopathy [33–36].

The association of hyper IgM and t(11;18) might have been derived from the CD40 pathway that causes secretion of IgM in B cells [37]. Among the known fusion genes specific to MALT lymphoma, this *API2* is the sole partner gene that is a degradative ubiquitin ligase to downstream signaling gene of CD40 [38, 39]. *API2* gene is thought to be involved in non-canonical NF-κB signaling, CD40, different from other fusion

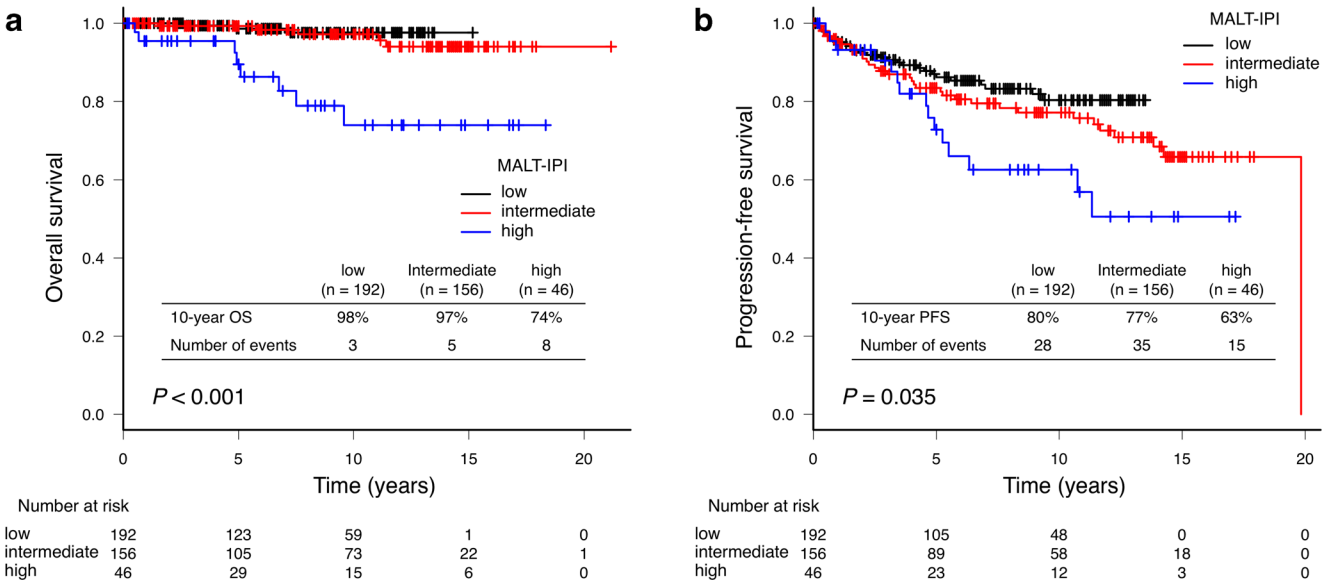

Fig. 3 Survival curves of the patients who were assessed for the MALT-IPI ($n = 394$). **a** Overall survival (OS) and **b** progression-free survival (PFS); HR, hazard ratio; CI, confidence interval

partner gene, or mutated gene that can cause MALT lymphoma. In the CD40 signaling, which preferentially uses non-canonical NF-κB signaling, TRAF2 is polyubiquitinated by API2, through the BIR domain. The API2/MALT1 fusion gene keeps the BIR domain of API2, which interacts with TRAF2 and activates non-canonical NF-κB pathway downstream of CD40.

CD40 signaling can cause not only increased level of IgM secretion but also class switch [37, 40], which can explain again the in vivo class switch shown in this study. Alternatively, but not mutually exclusive, caspase domain of the fusion gene might be involved. *MALT1* gene can activate canonical NF-κB pathway once CD40 signaling is on [41]. Indeed, study on IgM level in MALT lymphoma cases with t(14;18), in which *MALT1* gene is over expressed, will tell the involvement of the MALT1 caspase domain; involvement of MALT1 caspase domain in the pathogenesis of MALT lymphoma is demonstrated by the previous report stating that the defective caspase domain of MALT1 causes defective splenic marginal zone B cells in mice [42].

We unexpectedly found that a subset of MALT lymphoma patients with t(11;18) showed immunoglobulin class switches. The order of the switch followed that of normal lymphocytes; all patients initially showed IgM expression and later switched to IgA or IgG. This has already been reported in a case of gastric and intestinal extranodal plasmacytoid lymphoma [43].

The class switch is known to be caused by activation-induced cytidine deaminase (AID). Immunoglobulin gene analyses of MALT lymphoma cases show somatic hypermutation [44, 45]. As AID causes hypermutation of immunoglobulin genes, it is conceivable that the tumor cells with hypermutation have a tendency to class switch. The class switch specifically shown in cases with t(11;18) might be reminiscent of AID activation in B cells. This is in contrast to the previous study, which showed impaired class switch recombination in WM [46].

In conclusion, our study confirms the previous findings that t(11;18)-positive MALT lymphoma is characterized by high incidence of monoclonal gammopathy, especially of the IgM subtype, a significantly higher recurrence rate, but with favorable overall outcome. Among the heterogeneities of MALT lymphoma with predictable benign prognosis, it is noteworthy to identify this distinct subtype carrying API2/MALT1.

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Author contributions K. Toyoda, Y.K., and A.M.M. designed the study; K. Toyoda and A.M.M. analyzed the data; K. Toyoda and Y.K. wrote the paper; A.M.M., J.N., T.S., S.Y., N.Y., S.M., S.F., W.M., D.M., H.T., and K. Tobinai reviewed and approved the final version of the manuscript.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval This study was performed under the Institutional Review Board approvals from The National Cancer Center Hospital and conducted in accordance with the Declaration of Helsinki. For this type of study, formal consent is not required.

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