Involvement of the Chromosomal Translocation t(11;18) in Some Mucosa-Associated Lymphoid Tissue Lymphomas and Diffuse Large B-Cell Lymphomas of the Ocular AdnexaEvidence from Multiplex Reverse Transcriptase-Polymerase Chain Reaction and Fluorescence In Situ Hybridization on Using Formalin-Fixed, Paraffin-Embedded Specimens

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The chromosomal translocation t(11;18) is a unique chromosomal aberration associated with mucosa-associated lymphoid tissue lymphoma. *API2* and *MALT1* genes have been identified around this translocation. We attempted to find chromosomal abnormalities focusing mainly on the t(11;18) translocation in formalin-fixed, paraffin-embedded tissues of ocular adnexal lymphoproliferative disorders using multiplex reverse transcriptase-polymerase chain reaction and/or two-color interphase fluorescence *in situ* hybridization. By these methods, the t(11;18) translocation was detected in 1 of 8 patients with reactive lymphoid hyperplasia (13%), 3 of 23 with mucosa-associated lymphoid tissue lymphoma (13%), and 2 of 14 with diffuse large B-cell lymphoma with/without mucosa-associated lymphoid tissue lymphoma (14%). Moreover, we performed fluorescence in situ hybridization analysis to detect any numerical aberration of chromosomes 3, 7, 12, and 18 on some specimens nonselectively. No numerical chromosomal abnormalities were detected in 3 cases of reactive lymphoid hyperplasia, whereas three of four cases of mucosa-associated lymphoid tissue lymphoma and all four cases of diffuse large B-cell lymphoma with/without mucosa-associated lymphoid tissue lymphoma components exhibited one or more abnormalities. These findings indicate a possibility that at least in the ocular adnexa, some diffuse large B-cell lymphomas are derived from mucosa-associated lymphoid tissue lymphomas.

KEY WORDS: Chromosomal translocation, Diffuse large B-cell lymphoma, Fluorescence *in situ* hybridization, Mucosa-associated lymphoid tissue lymphoma, Ocular adnexa, RT-PCR.

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Mucosa-associated lymphoid tissue (MALT) lymphoma was first described in 1983 by Isaacson and Wright (1). Since then, its clinicopathological features have been well characterized, and the REAL (2) and WHO classifications (3) have categorized it as a distinct lymphoma type. MALT lymphomas arise in numerous organs that lack native lymphoid

tissues but which acquire MALT associated with chronic inflammatory processes triggered by autoimmune phenomena and/or chronic infection. Recent studies have revealed the recurrent chromosomal aberration in MALT lymphomas: trisomies 3, 7, 12, and 18 (4–8); t(1;14)(p22;q32) (9, 10); and t(11;18)(q21;q21) (10–16). The chromosomal translocation t(11;18)(q21;q21) represents the most frequent structural chromosomal abnormality in MALT lymphoma, resulting in the production of *API2-MALT1* fusion transcripts (14–16). Interestingly, this translocation has not been detected in diffuse large B-cell lymphomas of the stomach, although some diffuse large B-cell lymphomas are known to be associated with MALT lymphoma (11, 16).

The ocular adnexa is a site frequently affected by MALT lymphoma, but chromosomal abnormalities of ocular adnexal lymphoproliferative disorders have not been well clarified yet. We previously reported clinicopathological data on these disorders (17). In this study, we attempted to clarify chromosomal abnormalities in ocular adnexal lymphoproliferative disorders such as reactive lymphoid hyperplasia, MALT lymphoma, and diffuse large B-cell lymphoma, mainly focusing on the t(11;18)(q21;q21) translocation.

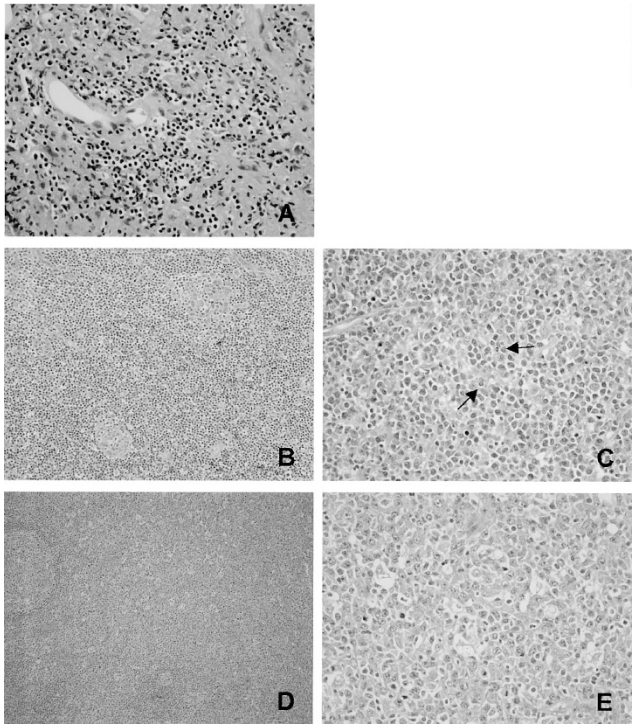

FIGURE 1. Reactive lymphoid hyperplasia (**A**) and primary MALT lymphoma with diffuse large B-cell lymphoma (**B–E**). **A** (Case 2); note infiltrating lymphoid cells show small cells and no atypia. **B, C** (Case 32), lesions of MALT lymphoma; note lymphoma cells show differentiate plasmacytes with Datcher bodies. **D, E** (Case 32), lesions of diffuse large B-cell lymphoma; note lymphoma cells show large cells and severe atypia.

MATERIALS AND METHODS

Cases

Formalin-fixed, paraffin-embedded tissue specimens of ocular adnexal lesions were retrieved from files dated between 1989 and 2000 of the Department of Pathology, Okayama University Medical School and from consultation files. Hematoxylin and eosin-stained sections were re-evaluated, and so we changed diagnosis from pseudolymphoma to reactive lymphoid hyperplasia in 7 cases, from diffuse lymphoma, medium-sized cell type to MALT lymphoma in 11 cases, and from diffuse lymphoma, mixed cell type to MALT lymphoma with diffuse large B-cell lymphoma in 1 case. Forty-five consecutive cases of lymphoproliferative disorders were chosen for this study: 8 cases of reactive lymphoid hyperplasia (Fig. 1A), 23 of MALT lymphoma, 2 of diffuse large B-cell lymphoma with MALT lymphoma (Fig. 1, B–D), and 12 of diffuse large B-cell lymphoma without MALT lymphoma. All patients were Japanese adults. The clinical features of each diagnostic category are summarized in Table 1.

The patient (Case 1) with reactive lymphoid hyperplasia died of non-Hodgkin's lymphoma, diffuse large B-cell lymphoma that developed in lymph nodes and the parotid glands but did not involve the orbit. MALT lymphoma was diagnosed not only histologically but also by confirming the clonality using immunohistochemical Ig light-chain restriction. Histological criteria described by Isaacson and Norton (18) were applied for diagnosis of MALT lymphomas. Immunoglobulin gene rearrangements were never detected in the cases of reactive lymphoid hyperplasia by PCR and/or Southern blotting analyses.

Fluorescence *In Situ* Hybridization

The interphase FISH assay was established by selecting YAC DNA clones flanking the breakpoint regions of 11q21 and 18q21 in the t(11;18)(q21;q21) translocation (19, 20). YAC clone 966e4 was chosen from the centromeric side of the 11q21 breakpoint. Similarly, YAC clones 943b8 and 845c5 were chosen from the telomeric and the centromeric sides of the 18q21 breakpoint, respectively. After amplification of human sequences by Alu-PCR (21), probes for FISH were generated by a nick translation kit with spectrum orange- and spectrum green-labeled d-UTP (Vysis Inc., Downers Grove, IL). FISH was performed on cells isolated from paraffin sections according to the standard protocols (22, 23). In normal interphase cells, hybridization resulted in close spatial relation of the differentially labeled YAC clones, y845c5 and y943b8, leading to two red/green signal pairs per nucleus, and in wide spatial

TABLE 1. Clinicopathological Features of Each Histological Category

Histology	Number	Gender (M/F)	Age		Bilateral	Involved Sites				DWD
			Range	Mean	Conjunctiva		LG	LS	Orbit	
Reactive lymphoid hyperplasia	8	5/3	35–70	53.1	5	0	6	0	2	0
MALT lymphoma	23	10/13	27–79	57.6	5	8	4	1	10	0
Diffuse large B-cell lymphoma	14	6/8	40–86	68.1	0	3	4	0	7	4

MALT = mucosa-associated lymphoid tissue; LG = lacrimal gland; LS = lacrimal sac; DWD = died with disease.
* Including diffuse large B-cell lymphoma and diffuse large B-cell lymphoma with MALT lymphoma.

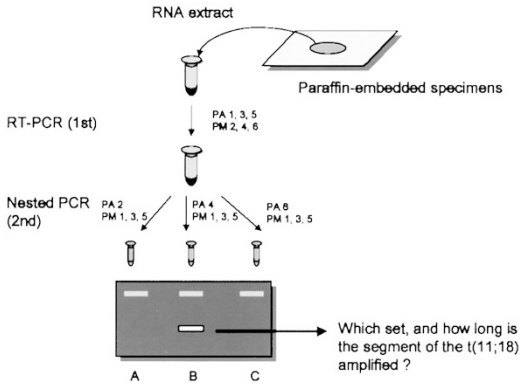

FIGURE 2. Flow diagram of multiplex reverse transcriptase-polymerase chain reaction

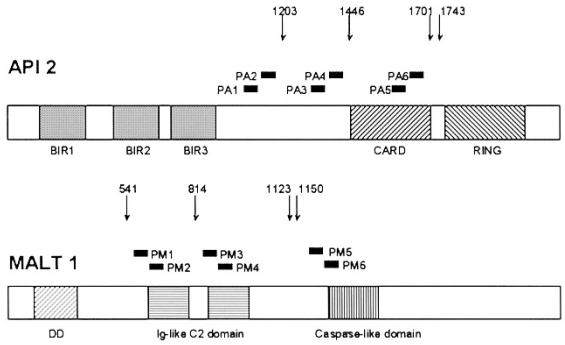

FIGURE 3. Locations of API2 and MALT1 breakpoints and primers for multiplex RT-PCR assay. The ***arrows*** indicate API2 and MALT1 breakpoints previously reported. Numbering is in accordance with the accession number L49432 for API2 and with the accession number AF130356 for MALT1.

relation of the differentially labeled YAC clones, y943b8 and y966e4, leading to two red signals and two green signals per nucleus. In cells carrying the t(11;18)(q21;q21) translocation, a derivative signal constellation with one red/green signal pair and separately spaced red and green signals per nucleus were observed, using each YAC clone pair. Centromere-specific probes (Vysis) of chromosomes 3, 7, 12, and 18 were used for analysis of numerical chromosomal aberration. To determine the cutoff level in normal interphase nuclei, specimens from the four lymph nodes served as a negative control. For evaluation of FISH analysis, 100–200 intact nuclei per case were observed on an Olympus BH2 fluorescence microscope.

Multiplex Reverse Transcriptase (RT)-PCR

API2-MALT1 fusion transcripts were detected by multiplex RT-PCR comprised of the first-round multiplex one-tube RT-PCR and three subsequent parallel multiplex nested PCRs, as described elsewhere (24). Briefly, total RNA was extracted from deparaffinized paraffin sections, and 5 mL of RNA solution was subjected to the first-round one-tube RT-PCR. Three different primer pairs (PA1-PM2, PA3-PM4, and PA5-PM6) were added to the reaction mixture containing Moloney murine leukemia virus reverse transcriptase (Life Technology, Tokyo, Japan), the deoxynucleotides, and TaqGOLD DNA polymerase (Applied Biosystems, Foster City, CA). After reverse transcription and PCR, the first-round RT-PCR product diluted with water to 1:16 was subjected to the three parallel second-round multiplex nested PCRs. Primers PA2, PM1, PM3, and PM5 were used to detect fusion genes possessing an API2 breakpoint at bp 1203 (second PCR-A); PA4, PM1, PM3, and PM5 were used for bp 1446 (second PCR-B); and PA6, PM1, PM3, and PM5 were used for bp 1701 or 1743 (second PCR-C; Figs. 2, 3, Table 2).

For the internal positive control, we amplified the ubiquitously expressed beta-actin mRNA.

RESULTS

The chromosomal translocation t(11;18)(q21;q21) was analyzed by FISH in eight cases of primary

TABLE 2. Oligonucleotide Sequences of Primers

Primer	Sequence
PA1	ttcatccgtcaagttcaagc
PA2	agccagttaccctcatctac
PA3	ttactcaatgcagaagatga
PA4	gaaataagggaagaggagag
PA5	caagagaactgattgatacg
PA6	attgcagccactgtattcag
PM1	cagccaagactgcctttgac
PM2	ttgaacaaaaggatgtccag
PM3	ggcatcagcttttgggaagt
PM4	actgtaaaaccaatgtgctg
PM5	aaaggctggtcagttgtttg
PM6	ttcctatcaaaagggcaacc
AC1	gagcaagagaggcatcct
AC2	cagtggtacggccagagg
AC3	tggagaaaatctggcaccac
AC4	gaggcgtacagggatagcac

PA1–6, AC1, and AC3, sense primers; PM1–6, AC2, and AC4, antisense primers.

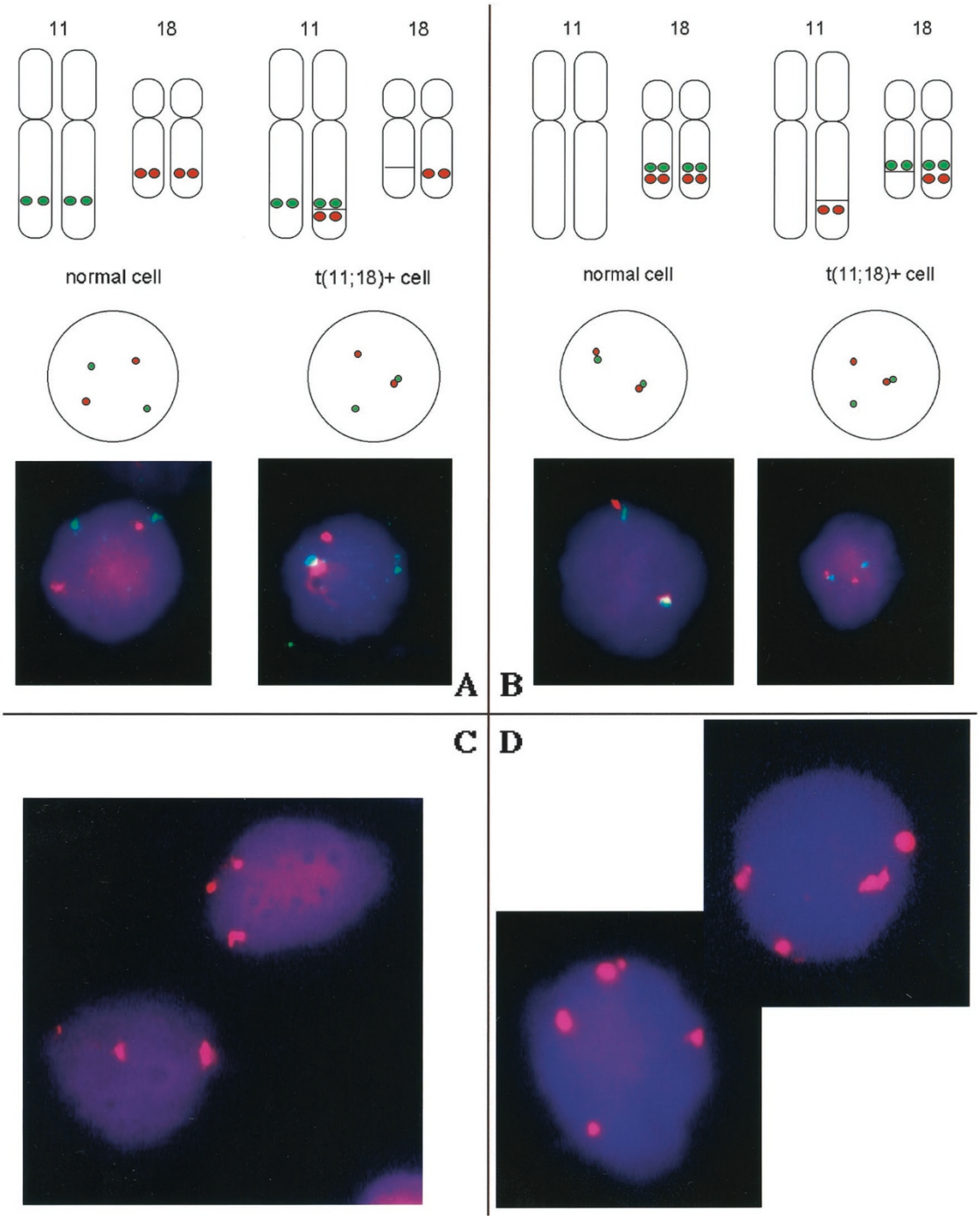

FIGURE 4. Two-color FISH for the t(11;18) (**A, B**) and FISH for numerical aberration of chromosomes (**C, D**). **A,** FISH for the t(11;18) using YAC clones y943b8 and y 966e4. The t(11;18)+ cells show one red/green signal pair, one red signal, and one green signal per nucleus (***right***). Normal cells show two red signals and two green signals per nucleus (***left***). Case 17. **B,** FISH for the t(11;18) using YAC clones y845c5 and y943b8. The t(11;18)+ cells show one signal pair, one red signal, and one green signal per nucleus (***right***). Normal cells show two signal pairs per nucleus (***left***). Case 39. **C,** FISH with chromosome 3 centromere-specific probe. Trisomy 3 is observed. Case 38. **D,** FISH with chromosome 18 centromere-specific probe. Tetrasomy 18 is observed. Case 36.

ocular adnexal malignant lymphomas (4 MALT lymphomas, 1 diffuse large B-cell lymphoma with MALT lymphoma and 3 diffuse large B-cell lymphomas without MALT lymphoma) and three cases of reactive lymphoid hyperplasia. FISH showed the t(11;18)(q21;q21) translocation in one of four cases of MALT lymphoma and in one of three cases of diffuse large B-cell lymphoma without MALT lymphoma (Fig. 4, A–B). Numerical aberration of chromosomes 3, 7, or 18 was detected in five of eight cases of malignant lymphoma examined by FISH (Fig. 4, C–D). Especially, all diffuse large B-cell lymphoma with or without MALT lymphoma exhibited polysomies. In contrast, only one of four cases of

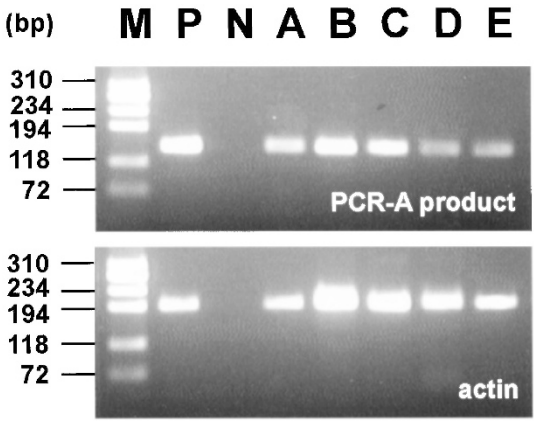

FIGURE 5. Reverse transcriptase-polymerase chain reaction analysis of lymphoproliferative disorders in the ocular adnexa. ***Lane M***, Phi × 174 DNA ***Hae***III digest (72, 118, 194, 234, 271, 281, 310 bp); ***Lane P***, positive control; ***Lane N***, negative control; ***Lane A,*** Case 2 (reactive lymphoid hyperplasia); ***Lane B***, Case 19 (MALT lymphoma); ***Lane C,*** Case 30 (MALT lymphoma); ***Lane D***, Case 37 (diffuse large B-cell lymphoma); ***Lane E***, Case 39 (diffuse large B-cell lymphoma).

MALT lymphoma demonstrated a trisomy. Reactive lymphoid hyperplasia had no apparent chromosomal abnormalities as tested.

RT-PCR was performed in 37 cases of primary ocular malignant lymphomas (23 cases of MALT lymphoma, 2 cases of diffuse large B-cell lymphoma with MALT lymphoma, and 12 cases of diffuse large B-cell lymphoma without MALT lymphoma) and 6 cases of reactive lymphoid hyperplasia. All cases examined show clear actin amplification as internal control. The t(11;18)(q21;q21) translocation was detected by RT-PCR in 4 of 37 cases of malignant lymphomas tested: 2/23 cases of MALT lymphoma (9%) and 2/12 cases of diffuse large B-cell lymphoma without MALT lymphoma (17%). RT-PCR also detected the t(11;18)(q21;q21) translocation in one of six cases of reactive lymphoid hyperplasia (17%). The t(11;18)(q21;q21) translocation was detected only with the second PCR-A, and the amplified PCR products were all the same size, 147 bp (Fig. 5). The results from the FISH and RT-PCR analyses are summarized in Table 3. FISH and/or RT-PCR disclosed the t(11;18)(q21;q21) translocation in one of eight cases of reactive lymphoid hyperplasia (13%), 3 of 23 cases of MALT lymphoma (13%), and 2 of 14 cases of diffuse large B-cell lymphoma with or without MALT lymphoma (14%).

DISCUSSION

Ott *et al.* (11) first described the t(11;18)(q21;q21) translocation as a frequent and specific chromosomal aberration in MALT lymphomas using a conventional cytogenetic analysis. However, conventional cytogenetic analysis requires fresh cell suspensions. In contrast, FISH and RT-PCR are useful tools to identify cytogenetic abnormalities in the interphase nuclei of formalin-fixed, paraffin-embedded tissues. The two-color FISH assay using *API2*- and *MALT1*-specific probes for the detection of t(11;18)(q21;q21) translocation was previously applied to MALT lymphomas of the stomach, lung, ocular adnexa, and other sites (12, 13). We also performed FISH analysis, but only for a limited number of cases because FISH requires cells isolated from relatively large paraffin sections.

RT-PCR for the detection of the t(11;18)(q21;q21) translocation has been described elsewhere (10, 14–16, 24), and the results of the analyses on the t(11;18) translocation in MALT lymphomas of the stomach, lung, and ocular adnexa found in the literature (10–16, 24) are summarized in Table 4. The incidence of t(11;18) translocation has been reported to be 10–72% in MALT lymphomas of the stomach and 56–100% in pulmonary cases. However the t(11;18) translocation was not detected in any of the cases of ocular adnexal MALT lymphoma, although the number of cases was rather small. In the present study, 23 cases of MALT lymphoma in the ocular adnexa were analyzed by FISH and/or RT-PCR, disclosing 3 cases (13%) positive for the t(11;18) translocation. This frequency is comparable to that of t(11;18)-positive gastric MALT lymphoma in Japan, which is much lower than that in European patients. In case 17, the t(11;18) translocation was detected by FISH, but not by RT-PCR. This is likely due to the difference in the sampling methods or selection of PCR primers. Then, we tried to perform RT-PCR analysis with other PCR primer sets (10) to know the possibilities of false negative of RT-PCR. By this additional experiment, t(11;18) was not detected using frozen section by RT-PCR with other primer sets. The t(11;18) translocation has been much more frequently observed in MALT lymphomas of the lung. MALT lymphoma is a distinct lymphoma subtype, but the pathogenesis or cytogenetic characteristics of MALT lymphomas may differ depending on the anatomical location and also possibly on the patient's environmental or racial background.

The t(11;18) translocation has not been detected in diffuse large B-cell lymphomas of the stomach (11, 16) a fact that has thrown doubt on the derivation of gastric diffuse large B-cell lymphomas from MALT lymphomas. The present study revealed the t(11;18) translocation in 2 of 12 cases of primary diffuse large B-cell lymphoma (17%) of the ocular adnexa, none of which had a residual MALT lymphoma component. This evidence may suggest the possibility that some diffuse large B-cell lymphomas of the ocular adnexa are derived from MALT lymphomas. However, two cases of diffuse large B-cell lymphoma with MALT lymphomas were negative for the t(11;18) translocation. Furthermore,

TABLE 3. Results of FISH and RT-PCR

Case Number	Sex	Age (yrs)	Diagnosis	Site	Follow-Up Time (months)	Status at Last Follow-Up	Molecular Analysis by Using PCR	Molecular Analysis by Southern Blotting	FISH	RT-PCR
1	M	35	RLH	Orbit	103	Died of NHL	Not clonal	n.d.	n.d.	−
2	M	62	RLH	LG	65	Alive	Not clonal	Not clonal	n.d.	A
3	F	70	RLH	LG	66	Alive	Not clonal	Not clonal	n.d.	−
4	M	50	RLH	Orbit	44	Alive	Not clonal	Not clonal	−	−
(4)						(Second biopsy)	Not clonal	Not clonal	−	n.d.
5	M	52	RLH	LG	−	Lost to follow-up	Not clonal	Not clonal	−	n.d.
6	M	43	RLH	LG	23	Alive	Not clonal	Not clonal	n.d.	−
7	F	44	RLH	LG	43	Alive	Not clonal	Not clonal	−	−
8	F	69	RLH	LG	54	Alive	Not clonal	Not clonal	n.d.	−
9	F	63	MALT	Orbit	120	Alive	n.d.	Clonal	n.d.	−
10	F	39	MALT	LG	16	Alive	Clonal	Clonal	−	−
11	M	76	MALT	LG	39	Alive	Not clonal	Not clonal	n.d.	−
12	M	61	MALT	Orbit	60	Alive	Not clonal	Not clonal	n.d.	−
13	M	56	MALT	Orbit	100	Alive	n.d.	Not clonal	n.d.	−
14	F	55	MALT	LS	98	Alive	Clonal	Not clonal	n.d.	−
15	F	64	MALT	Conj.	87	Alive	Clonal	Not clonal	n.d.	−
16	M	67	MALT	Conj.	64	Alive	Not clonal	Not clonal	n.d.	−
17	M	67	MALT	Orbit	87	Alive	Clonal	Clonal	t(11;18)	−
18	F	64	MALT	Conj.	84	Alive	Not clonal	Not clonal	n.d.	−
19	F	67	MALT	Orbit	18	Alive	Not clonal	Clonal	n.d.	−
20	M	71	MALT	Orbit	12	Alive	Not clonal	n.d.	n.d.	−
21	M	56	MALT	Orbit	7	Alive	Clonal	Not clonal	n.d.	−
22	F	27	MALT	Conj.	71	Alive	Clonal	n.d.	n.d.	−
23	F	57	MALT	LG	59	Alive	n.d.	n.d.	n.d.	−
24	F	57	MALT	Conj.	26	Alive	Clonal	n.d.	n.d.	−
25	M	61	MALT	Orbit	20	Alive	Clonal	Not clonal	n.d.	−
26	M	53	MALT	Conj.	27	Alive	Clonal	Clonal	−	−
27	F	60	MALT	Conj.	13	Alive	n.d.	n.d.	n.d.	−
28	M	79	MALT	Orbit	−	Lost to follow-up	n.d.	n.d.	trisomy 3	−
29	F	29	MALT	Conj.	6	Alive	n.d.	n.d.	n.d.	−
30	F	47	MALT	LG	12	Alive	n.d.	n.d.	n.d.	A
31	F	49	MALT	Orbit	37	Alive	n.d.	n.d.	n.d.	−
32	F	86	DLBCL+MALT	LG	11	Alive	Not clonal	n.d.	trisomy 18	−
33	F	65	DLBCL+MALT	Orbit	1	DWD	n.d.	n.d.	n.d.	−
34	M	80	DLBCL	Orbit	−	Lost to follow-up	n.d.	n.d.	n.d.	−
35	M	66	DLBCL	LG	4	DWD	n.d.	n.d.	n.d.	−
36	F	67	DLBCL	LG	111	Alive	Clonal	n.d.	trisomy 7+tetrasomy 18	−
37	F	64	DLBCL	Orbit	35	DWD	Clonal	n.d.	n.d.	A
38	M	74	DLBCL	LG	20	Died NED	n.d.	n.d.	trisomy 3	−
39	M	75	DLBCL	Conj.	30	Alive	Clonal	Clonal	t(11;18)+trisomy 18	A
40	M	56	DLBCL	Conj.	25	Alive	Not clonal	n.d.	n.d.	−
41	F	65	DLBCL	Orbit	39	Alive	n.d.	n.d.	n.d.	−
42	F	73	DLBCL	Orbit	19	Alive	n.d.	n.d.	n.d.	−
43	F	74	DLBCL	Conj.	−	Lost to follow-up	n.d.	n.d.	n.d.	−
44	M	69	DLBCL	Orbit	2	Alive	n.d.	n.d.	n.d.	−
45	F	40	DLBCL	Orbit	18	DWD	n.d.	n.d.	n.d.	−

RLH = reactive lymphoid hyperplasia; MALT = mucosa-associated lymphoid tissue lymphoma; DLBCL = diffuse large B-cell lymphoma; LG = lacrimal gland; LS = lacrimal sac; Conj. = conjunctiva; n.d. = not done; − = negative; A = positive for RT-PCR product A (PCR-A); DWD = died with the disease; NED = no evidence of the disease.

TABLE 4. Incidence of the t(11;18) Chromosomal Translocation in MALT Lymphomas

Authors	Number of Positive Cases/Number of Cases Examined (%)			Method	Reference
	Stomach	Lung	Ocular adnexa		
Ott *et al.*	4/10 (40)	2/2 (100)	0/1 (0)	Karyotype	11
Rosenwald *et al.*	7/21 (33)	1/1 (100)	0/3 (0)	FISH	12
Dierlamm *et al.*	6/24 (25)	—	0/5 (0)	FISH	13
Kalla *et al.*	13/18 (72)	2/2 (100)	—	FISH/RT-PCR	14
Motegi *et al.*	1/11 (10)	5/9 (56)	—	RT-PCR	15
Beans *et al.*	11/23 (48)	—	—	RT-PCR	16
Inagaki *et al.*	1/8 (13)	3/4 (75)	—	RT-PCR	24
Liu *et al.*	19/56 (34)	4/7 (57)	0/1 (0)	RT-PCR	10
The present study	—	—	3/23 (13)	FISH/RT-PCR	—

only a small portion of MALT lymphomas of the ocular adnexa showed the t(11;18) translocation. Thus, further studies are required before drawing a definite conclusion. In addition, polysomies were observed more frequently in diffuse large B-cell lymphomas than in MALT lymphomas. However

the limited number of cases examined did not allow for a statistical analysis.

In reactive lymphoid hyperplasia of the ocular adnexa, only one case demonstrated the t(11;18) translocation by RT-PCR, but the rearrangement of immunoglobulin heavy chain genes was not detected by PCR using primers directed to the framework 2 region and to the joining region (previous report [17]). RT-PCR is so sensitive that it could detect only a small number of t(11;18)-positive cells among lymphoid cells in reactive lymphoid hyperplasia. This suggests that the t(11;18) translocation is a manifestation of the spectrum of diseases and so that patients with reactive lymphoid hyperplasia need to be followed as MALT lymphomas may be derived from reactive lymphoid hyperplasia.

In conclusion, the t(11;18)(q21;q21) translocation was detected in 13% of reactive lymphoid hyperplasia cases, 13% of MALT lymphoma cases, and 14% of diffuse large B-cell lymphoma cases with/without MALT lymphoma components by FISH and/or multiplex RT-PCR using formalin-fixed, paraffin-embedded materials. At least in the ocular adnexa, some MALT lymphomas and diffuse large B-cell lymphomas are positive for t(11;18)(q21;q21) translocation. These results suggest that some diffuse large B-cell lymphomas may arise from MALT lymphomas.

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Book Review

Smith CUM: Elements of Molecular Neurobiology, 3rd Edition, 630 pp, Hoboken, NJ, John Wiley & Sons, 2002 ($165.00).

A concise and current textbook of the basic concepts in molecular neurobiology, this book provides the foundation for an understanding of the molecular basis of neurobiology. It is a wealth of basic information and a serious starting point for undergraduate students, neuroscience students, molecular biologists, pharmacologists, and researchers who want a concise introduction to the field. The success of the book is illustrated by the fact that this is the third edition since 1989. The author should be congratulated not only for the valuable integration of the important aspects of molecular biology in neuroscience but also for relatively early recognition of the need for a modern textbook on this rapidly developing field.

The main feature of this book is the well-balanced amount of information provided in each chapter. Well-structured and up-to-date chapters, glossary, five appendices (Molecules and Consciousness, Units, Data, Genes, Physical Models of Ion Conduction), an index of neurological diseases, and a very helpful high-yield bibliography (excellent selection of the most important reviews) make this book really complete and one of the best sources for learning. The bibliography also provides Web sites relevant for each chapter. It is a new and very useful feature and provides a good introduction to further study. Among many other innovations, it represents the inventive and modern author's approach. The book is well-illustrated, and it successfully presents complex ideas visually. Some continuing controversial issues in neuroscience are represented in a fair and unbiased way. Basic concepts as well as recent developments in clinical and basic neuroscience likely to assist in the understanding of the relevant neurological disorders are included and well-explained. All these features are especially important for students.

I recommend this book because it brings together a wide range of current concepts in a compact and well-edited volume. This unique, easy to read book serves as an excellent source for studying as well as a ready and accessible reference that will be a great help to its readers. It already has a well-earned place on the neuroscience students' reference shelf.

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