Frequency of Chromosomal Aberrations Involving *MALT1* in Mucosa-Associated Lymphoid Tissue Lymphoma in Patients with Sjögren's Syndrome

Berthold Streubel,[1] Daniela Huber,[1] Stefan Wöhrer,[2] Andreas Chott,[1] and Markus Raderer[2]

Departments of [1]Pathology and Internal Medicine I and [2]Division of Oncology, Vienna General Hospital, University of Vienna, Vienna, Austria

ABSTRACT

Purpose: **Mucosa-associated lymphoid tissue (MALT) lymphoma develops in the context of longstanding antigenic stimulation such as infection with *Helicobacter pylori* or autoimmune disease, including Sjögren's syndrome (SS). Recently, two chromosomal aberrations involving the *MALT1* gene, *i.e.*, t(11;18)(q21;q21) and t(14;18)(q32;q21) have been reported as genetic events specific for MALT lymphoma. In view of the association between SS and the development of MALT lymphoma, we have analyzed the frequency of t(11;18)(q21;q21) and t(14;18)(q32;q21) in patients with MALT lymphomas arising in the background of SS.**

Experimental Design: **A retrospective analysis of patients diagnosed with MALT lymphoma and SS was performed. The t(11;18)(q21;q21) was analyzed using reverse transcriptase-PCR, whereas t(14;18)(q32;q21) was assessed by two-color interphase fluorescence *in situ* hybridization.**

Results: **Twenty-six patients (20 female and 6 male) with MALT lymphoma and SS could be identified. The lymphoma was located in the parotid ($n = 14$), orbit ($n = 2$), and submandibular gland ($n = 1$), whereas 9 patients had gastric MALT lymphoma. Seven of 26 patients (27%) harbored t(11;18)(q21;q21). Interestingly, only 1 of 17 patients (6%) with extragastrointestinal lymphoma was positive, as opposed to 6 of 9 patients (67%) with gastric MALT lymphoma. Four of 26 patients were positive for t(14;18)(q32;q21): 3 of 17 extragastrointestinal (18%) and 1 of 9 gastric lymphomas (11%).**

Conclusions: **The overall frequency of *MALT1* rearrangement appears to be low in patients with extragastrointestinal MALT lymphoma associated with SS. By contrast, *MALT1* rearrangement was demonstrated in 7 of 9 patients (78%) with gastric MALT lymphoma and SS. This finding may explain at least in part why gastric MALT lymphomas in patients with SS are refractory to *H. pylori* eradication therapy.**

INTRODUCTION

Mucosa-associated lymphoid tissue (MALT) lymphoma is a distinct lymphoma entity with unique features (1, 2). One of the most striking clinical characteristics is the association of MALT lymphoma with chronic antigenic stimulation, as exemplified by *Helicobacter pylori* infection in patients with gastric MALT lymphoma (2, 3). Although the large majority of cases arise in the stomach, MALT lymphomas may be encountered in virtually every organ of the human body (2, 4), with a predilection for the salivary glands and the lung.

An association between various autoimmune conditions and the occurrence of lymphoproliferative diseases has repeatedly been reported previously (5). Especially in case of autoimmune thyroiditis and Sjögren's syndrome (SS), a high risk for the development of MALT lymphomas in the primarily affected organs has been demonstrated. Accordingly, a 67-fold increased risk for thyroid MALT lymphoma and a 44-fold increased risk for parotid lymphoma is being attributed to autoimmune thyroiditis and SS (6, 7), and 1 in 5 deaths in patients with primary SS is due to the development of lymphoma (8).

Several genetic aberrations of MALT lymphoma have been identified, some of which appear to play an important role in the pathogenesis and also influence the prognosis of the disease. Two of these changes involve the *MALT1* gene located on chromosome 18. The t(11;18)(q21;q21) is considered to be specific for MALT lymphomas because it has not been found in nodal and splenic marginal zone B-cell lymphomas or other types of lymphoma (9, 10). This translocation results in the synthesis of the *API2-MALT1* fusion protein, which has recently been shown to activate nuclear factor-κB, a transcription factor for a number of survival-related genes (11). Up-regulation of these molecules promotes cellular proliferation and resistance to apoptotic signals. As a consequence, patients with gastric MALT lymphoma carrying t(11;18)(q21;q21) have been reported to be largely resistant to eradication of *H. pylori* and display a more aggressive clinical course (11).

Recently, we have reported the occurrence of t(14;18)(q32;q21) involving *IGH* and *MALT1* in patients with MALT lymphomas of the liver, skin, salivary glands, and ocular adnexa (12). It was neither detected in gastric, intestinal, pulmonary, and thyroid lymphomas nor in splenic marginal zone lymphomas. Although the potential function of this particular translocation in the pathogenesis of MALT lymphomas has not yet been elucidated, these findings together with the data published on t(11;18)(q21;q21) suggest *MALT1* rearrangements in up to 50% of all patients with MALT lymphoma.

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Requests for reprints: Andreas Chott, Department of Pathology, Vienna General Hospital, Waehringer Guertel 18-20, A-1090 Vienna, Austria. Phone/Fax: 43-1-4053402; E-mail: andreas.chott@akh-wien.ac.at.

A study from our institution has demonstrated an impaired response rate in patients with gastric MALT lymphoma and an additional autoimmune disease (AD) despite successful *H. pylori* eradication (13). Among these 6 patients initially described, three had gastric MALT lymphoma and a history of SS, suggesting AD to be an independent factor in the development of gastric MALT lymphoma. However, no analysis of genetic events involving *MALT1*, *i.e.,* t(11;18)(q21;q21) and t(14;18)(q32;q21), in MALT lymphoma associated with SS has been performed thus far. This has prompted us to investigate the frequency of t(11;18)(q21;q21) and t(14;18)(q32;q21) in MALT lymphomas of various localizations arising in patients with SS.

MATERIALS AND METHODS

Patients. A retrospective single-center analysis of patients diagnosed with MALT lymphoma and a history of SS was performed. The information on lymphoma diagnoses was based on entries in the Vienna Lymphoma Registry between 1997 and November 2002, which was searched for all cases identified as having MALT lymphoma. All patients enrolled in this study were staged according to our extensive protocol (14) and treated at our institution with full clinical information available. Eight patients, all of whom with MALT lymphoma of the parotid, have been part of a previous study (12). Information analyzed included the histological diagnosis, localization of the lymphoma, staging, and the presence of SS. The diagnosis of SS was based on characteristic clinical symptoms, *i.e.,* presence of mouth and/or eye dryness, as well as additional features such as a positive lip biopsy or serological changes as required in the recently updated United States-European criteria (15). Assessment of clinical and immunological parameters to diagnose an underlying autoimmune condition is routinely performed since 1997 at our institution in all patients with a diagnosis of MALT lymphoma. Only formalin-fixed, paraffin-embedded specimens were available. The presence of tumor cells was evaluated in each tissue block on H&E-stained sections cut before and after the sections used for reverse transcriptase-PCR or fluorescence *in situ* hybridization (FISH). Only blocks containing >50% lymphoma cells were analyzed.

Reverse Transcriptase-PCR for *API2-MALT1* Fusion Transcripts. Before the molecular investigations, the histological diagnosis of MALT lymphoma was reassessed according to the criteria as outlined by Isaacson *et al.* (1) in the WHO classification. RNA was isolated from formalin-fixed, paraffin-embedded lymphoma tissues obtained either by endoscopic biopsies or surgery. Total RNA was extracted from 10-μm sections with a high pure RNA paraffin kit (Roche Diagnostics, Mannheim, Germany). First-strand cDNA was synthesized from 1 μg of total RNA with a superscript first-strand synthesis system (Invitrogen, Carlsbad, CA) using random hexamers as primers. For evaluation of t(11;18)(q21;q21), reverse transcriptase-PCR was performed according to Inagaki *et al.* (16) with one difference: first round reverse transcriptase-PCR products were amplified in a second round separately and not as multiplex nested PCRs. β-*Actin* was amplified as a positive internal control.

FISH Analysis. Formalin-fixed, paraffin-embedded tissues were screened by FISH for t(14;18)(q32;q21) involving *IGH* and *MALT1*. For a reliable interpretation of the hybridization signals, we preferred the analysis of single cell suspensions over thin sections. After deparaffinization in xylene, two 30-μm thick slices were incubated for 25 min in 4% pepsin (pH 1.5) at 37°C. After a rapid wash in PBS, cells were incubated for 30 min in 0.075 M KCl and fixed twice in methanol/acetic acid (3/1) and dropped on slides. FISH was performed on interphases with a probe spanning the *MALT1* gene and flanking regions (PAC 152M5; Ref. 17) and an *IGH* probe (BAC158A2; Ref. 18) picked from a bacterial artificial chromosome library. The *IGH* probe was directly labeled with SpectrumGreen, the *MALT1* probe with SpectrumOrange by nick translation (Vysis, Downer's Grove, IL). A t(14;18) involving *IGH* and *MALT1* would result in a split orange *MALT1* signal with fusion to a green *IGH* signal. Five hundred cells were analyzed in each case. FISH procedure was performed as described elsewhere (12). The cutoff value for the diagnosis of a rearrangement involving *IGH* and *MALT1* was 5.3%, which is above the mean percentage of cells with a false-positive signal constellation plus 3 SDs, as assessed on tissue from 20 reactive lymph nodes processed as described for the lymphomas. Moreover, in all t(14;18)(q32;q21)+ lymphomas, verification of the rearrangement was performed with dual color break apart rearrangement probes for *IGH* (Vysis) and *MALT1* (12). As a result of this probe design, any translocation with a breakpoint at *IGH* or *MALT1* should produce separate orange and green signals.

On the single cell suspensions of 12 patients with MALT lymphoma of the salivary gland and no *MALT1* rearrangement, additional FISH was performed with probes for *IGH* and *BCL2* (Vysis). The orange *BCL2* probe covers the entire *BCL2* gene and additionally 250 kb both 5′ and 3′ of the gene. The 1.5-Mb green *IGH* probe covers the entire *IGH* locus. A t(14;18) involving *IGH* and *BCL2* would therefore result in one single green, one single orange, and two green/orange fusion signals in interphases. The cutoff value was 3.7%.

RESULTS

A total of 26 patients with MALT lymphoma and a clear-cut diagnosis of SS according to the criteria as outlined above (15) was identified (Table 1). As expected, the majority of patients were female (20 female and 6 male) and were aged between 31–80 years. Fifteen patients had lymphoma located in the salivary glands (parotid in 14, submandibular in 1 case), 2 had MALT lymphoma involving the lacrimal gland, whereas 9 patients suffered from gastric MALT lymphoma restricted to the stomach (stage EI disease). In all 9 cases with gastric lymphoma, evidence for *H. pylori* infection was present either histologically or serologically.

The reference gene β-*actin* was successfully amplified by reverse transcriptase-PCR in all 26 patients. In total, 7 patients (27%) were found to harbor t(11;18)(q21;q21). Interestingly, only 1 of 17 patients (6%) with extragastrointestinal lymphoma was found to be positive, whereas 6 of 9 patients (67%) with MALT lymphoma of the stomach had a positive reverse transcriptase-PCR for t(11;18)(q21;q21; Fig. 1). The breakpoints for *API2* (GenBank accession no. NM_001165) were at nucleic acids 2345 in 6 cases and at 2642 in 1 case; in *MALT1*(AF130356), it varied from 541 (patients 1 and 2), 814

Table 1 Patient characteristics and results of reverse transcriptase-PCR and fluorescence *in situ* hybridization analyses

Case	Age/Sex	Site	t(11;18)	Breakpoint *API2*	Breakpoint *MALT1*	t(IGH;MALT1)	t(IGH;BCL2)
1	65/F	Stomach	Pos	2345	541	n.d.	n.d.[a]
2	64/F	Stomach	Pos	2345	541	n.d.	n.d.
3	80/F	Stomach	Pos	2345	814	n.d.	n.d.
4	55/F	Stomach	Pos	2345	1123	n.d.	n.d.
5	36/F	Stomach	Pos	2345	1123	n.d.	n.d.
6	81/M	Stomach	Pos	2345	1151	n.d.	n.d.
7	56/F	Stomach	Neg			Neg	n.d.
8	64/F	Stomach	Neg			Neg	n.d.
9	76/M	Stomach	Neg			Pos.	n.d.
10	31/M	Parotid	Pos	2642	814	n.d.	n.d.
11	46/F	Parotid	Neg			Neg	Neg
12	63/F	Parotid	Neg			Neg	Neg
13	40/F	Parotid	Neg			Neg	Neg
14	47/F	Parotid	Neg			Neg	Neg
15	45/F	Parotid	Neg			Neg	Neg
16	68/F	Parotid	Neg			Neg	Neg
17	51/F	Parotid	Neg			Neg	Neg
18	48/M	Parotid	Neg			Neg	Neg
19	38/M	Parotid	Neg			Neg	Neg
20	51/M	Parotid	Neg			Neg	Neg
21	31/F	Parotid	Neg			Neg	Neg
22	78/F	Submandibular	Neg			Neg	Neg
23	37/F	Parotid	Neg			Pos	n.d.
24	50/F	Parotid	Neg			Pos	n.d.
25	70/F	Lacrimal	Neg			Pos	n.d.
26	39/F	Lacrimal	Neg			Neg	n.d.

[a] n.d., not determined.

(patients 3 and 10), 1123 (patients 4 and 5), and 1151 (patient 6; Table 1).

Screening for a rearrangement of *MALT1* by a t(14;18)(q32;q21) was performed using dual-color FISH (Fig. 2). In total, t(14;18)(q32;q21) was found in 4 patients (Table 1). The percentage of tumor cells evaluated in each tissue block on H&E-stained slides correlated with the number of cells with t(14;18)(q32;q21) assessed by the three independent FISH assays (*IGH/MALT1* dual color fusion, *IGH* dual color break apart, and *MALT1* dual color break apart). Three t(14;18)(q32;q21)+ tumors were of extragastrointestinal origin (two parotid and one lacrimal MALT lymphoma), whereas one originated in the stomach.

In 12 patients with MALT lymphoma of the salivary glands, rearrangements of *MALT1* either by a t(11;18)(q21;q21) or t(14;18)(q32;q21) were absent. These patients were additionally tested for t(14;18)(q32;q21) involving *IGH* and *BCL2*. All 12 patients were negative for *IGH/BCL2* rearrangement (Table 1).

DISCUSSION

t(11;18)(q21;q21) is found in MALT lymphomas arising at a variety of mucosal sites and is clinically important in gastric MALT lymphoma. The significance of analyzing t(11;18)(q21;q21) in gastric MALT lymphoma is underlined by its association with advanced disease and resistance to *H. pylori* eradication therapy (19). Studies using reverse transcriptase-PCR in comprehensive series of patients have demonstrated t(11;18)(q21;q21) in 24–40% of unselected gastric MALT lymphomas (20–25). However, these studies did not discriminate between tumors arising from proliferating B-cell populations induced by *H pylori* infection or originating in the background of AD. Although salivary gland lymphomas arising in patients with AD have repeatedly been recognized, the occurrence of primary gastric MALT lymphoma in such patients has not been given due consideration. To our knowledge, no prospective systematic screening for autoimmune conditions in patients with (gastric) MALT lymphomas has been reported in the literature. As of the beginning of 1997, at our institution, all patients with a diagnosis of MALT lymphoma irrespective of localization are evaluated clinically and serologically for autoimmune conditions, including SS. Because this has not consistently been done before, one might speculate that previous series have overlooked such an association.

In the present study, 9 primary gastric MALT lymphomas in patients with SS were investigated for t(11;18)(q21;q21). According to a rigorous staging system applied at our institu-

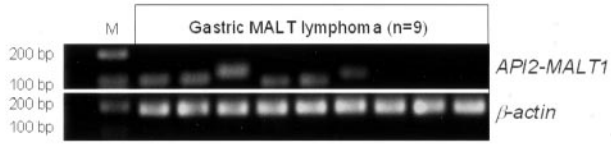

Fig. 1 Reverse transcriptase-PCR detection of *API2-MALT1* fusion transcripts in gastric mucosa-associated lymphoid tissue (MALT) lymphomas of patients with Sjögren's syndrome. The *top panel* shows the reverse transcriptase-PCR results for the *API2-MALT1* fusion transcripts. The breakpoints of the 6 t(11;18)+ cases are listed in Table 1. The reference gene β-*actin* was successfully amplified in all 9 cases (*bottom panel*).

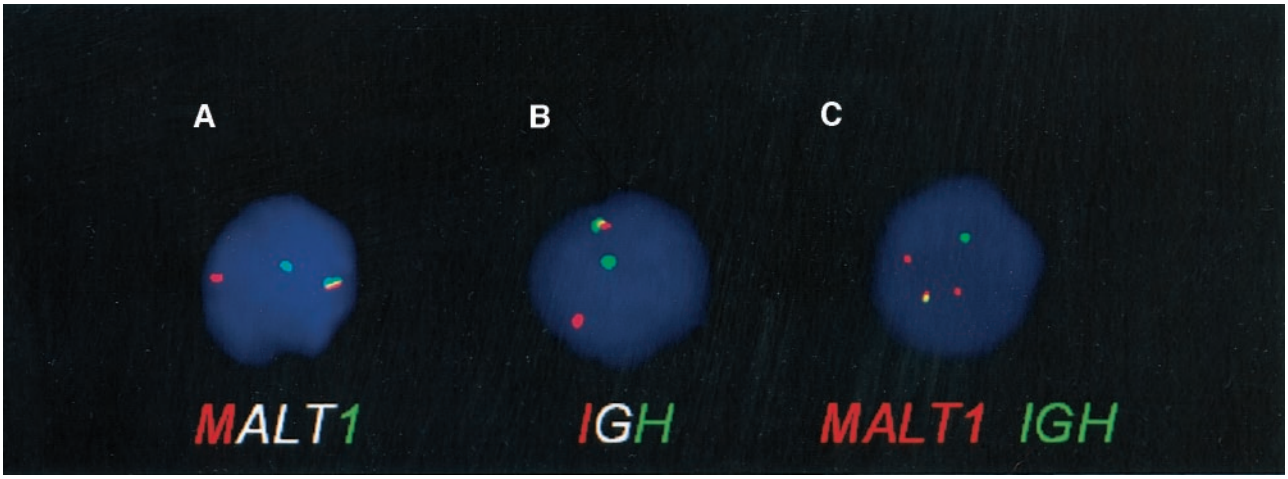

Fig. 2 Two-color fluorescence *in situ* hybridization to interphase nuclei isolated from paraffin-embedded tissue for the detection of the t(14;18)(q32;q21) involving *MALT1*. The orange PAC 117B5 (centromeric to *MALT1*) and green PAC 59N7 (telomeric to *MALT1*) show separate signals on an interphase nucleus of a t(14;18)(q32;q21)+ gastric mucosa-associated lymphoid tissue lymphoma (*A*); the same hybridization pattern is observed with probes flanking the joining segments and switch sequences of *IGH* (*B*), thus demonstrating *MALT1* and *IGH* rearrangements, respectively. In *C*, the green *IGH* signal is fused to a split *MALT1* signal providing an orange fusion signal confirming the t(14;18)(q32;q21).

tion, secondary spread from extragastric lymphoma can be ruled out almost with certainty. All of these patients had evidence of infection with *H. pylori*. Remarkably, 67% of these lymphomas were t(11;18)(q21;q21)+, which is a much higher percentage than reported in series from unselected cases of *H. pylori*-positive gastric MALT lymphomas and much higher than the 29.9% (20 of 69 cases) at our institution (unpublished data). At the moment, we cannot offer a definite explanation for this finding. Speculatively, MALT lymphoma cells in patients with SS in the context of *H. pylori* infection might be more susceptible to acquire the t(11;18), and the acquisition might occur at an earlier clinical stage of the disease. It is noteworthy in this regard that all 9 SS-associated gastric MALT lymphomas were so-called early lymphomas and thus confined to the mucosa and submucosa of the gastric wall.

As opposed to gastric and pulmonary MALT lymphomas, t(11;18)(q21;q21) is found at much lower frequencies in salivary gland and orbital tumors (9, 21, 22). Similarly, only one of the extragastrointestinal MALT lymphomas in our cohort of a patient with SS, a parotideal MALT lymphoma, revealed t(11;18)(q21;q21).

Apart from a fusion with *API2*, *MALT1* has recently been shown to be rearranged with *IGH* (12, 26, 27). This novel translocation was found in MALT lymphomas of the liver (4 of 4 cases), skin (3 of 11), ocular adnexa (3 of 8), and salivary glands (2 of 11), whereas 10 MALT lymphomas of the stomach and 9 of the intestine were negative (12). Moreover, it was demonstrated that t(11;18)(q21;q21) and t(14;18)(q32;q21) were mutually exclusive. In the present series, 1 of 2 MALT lymphomas of the ocular adnexa and 2 of 15 salivary gland MALT lymphomas carried t(14;18)(q32;q21). Interestingly, a t(11;18)(q21;q21)-negative MALT lymphoma of the stomach showed a rearrangement of *IGH* and *MALT1*, representing the first observation of a t(14;18)(q32;q21) in a gastric MALT lymphoma. Taken together, *MALT1* translocation either t(11;18)(q21;q21) or t(14;18)(q32;q21) occurred in 7 of 9 (78%) of gastric MALT lymphomas of SS patients.

In two previous studies of lymphomas in patients with SS, t(14;18)(q32;q21) was detected by PCR (28, 29). In these patients, however, *BCL2* and not *MALT1* was juxtaposed to *IGH*. *BCL2* rearrangements are highly associated with follicular lymphoma but are absent in MALT lymphoma (30, 31). In one of these studies, 1 of 8 SS patients had a *BCL2* translocation (28). This patient suffered from a pulmonary MALT lymphoma, which showed rapid transformation into a diffuse large B-cell lymphoma with consecutive nodal involvement, which also harbored t(14;18)(q32;q21). In the other study (29), *BCL2* translocations were detected in 5 of 7 SS-associated B-cell lymphomas involving the salivary glands. However, the exact histological classification of these lymphomas was not provided. Our assay for the detection of the t(14;18)(q32;q21) involving *IGH* and *MALT1* would not detect the t(14;18)(q32;q21) involving *BCL2* despite localization at the same chromosomal band. We therefore performed a FISH assay with probes for *BCL2* and *IGH*, which should disclose t(14;18) generated by *BCL2* breakpoints of major breakpoint and minor cluster regions as well as by additional breakpoints. All 12 cases negative for *MALT1* rearrangements were negative for t(14;18)(q32;q21) involving *BCL2*.

To summarize, the frequency of translocations involving *MALT1* appears to be low in patients with extragastrointestinal MALT lymphoma associated with SS. By contrast, *MALT1* rearrangement is frequently present in patients with gastric MALT lymphoma and SS (78%), which might explain at least in part why gastric MALT lymphomas in patients with AD are largely resistant to *H. pylori* eradication therapy (13).

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