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Mucosa-Associated Lymphoid Tissue (MALT) Lymphoma

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1. Introduction

1.1 Definition

Extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma) is an extranodal lymphoma composed of morphologically heterogeneous small B-cells including marginal zone (centrocyte-like) cells, cells resembling monocytoid cells, small lymphocytes, and scattered immunoblasts and centroblast-like cells. There is plasma cell differentiation in a proportion of the cases. The infiltrate is in the marginal zone of reactive B-cell follicles and extends into the interfollicular region. In epithelial tissues, the neoplastic cells typically infiltrate the epithelium forming lymphoepithelial lesions. (Swerdlow et al., 2008) (Isaacson et al., 2004)

1.2 Epidemiology

MALT lymphoma accounts for 7% of all newly diagnosed lymphomas and is therefore one of the more common types of lymphoma (Swerdlow et al., 2008). Most cases occur in adults with a median age of 61 and a slight female preponderance (male:female ratio 1:1.2). (Anon, 1997) There appears to be a higher incidence of gastric MALT lymphomas in north-east Italy (Doglioni et al., 1992) and a special subtype previously known as alpha heavy chain disease and now called immunoproliferative small intestinal disease (IPSID) occurs in the Middle East (Pinkel, 1998), the Cape region of South Africa (Price, 1990) and a variety of other tropical and subtropical locations.

1.3 Etiology

MALT lymphoma is a unique tumor in that it originates from acquired MALT associated with chronic inflammation or autoimmune responses, e.g. *Helicobacter pylori* (*H. pylori*)–associated chronic gastritis, Hashimoto's thyroiditis, and Sjögren's syndrome (Swerdlow et al., 2008, Isaacson, 1999a). MALT lymphoma affects various organs, with the stomach being the most frequently involved (Swerdlow et al., 2008, Isaacson, 1999a, 1999b). Interestingly, the majority of gastric low-grade MALT lymphoma cases, those proven to be neoplastic by detection of monoclonal rearrangement in immunoglobulin heavy chain (IgH) genes, regress after eradication of *H. pylori* (Wotherspoon et al., 1993, Thiede et al., 2000).

1.4 Management

MALT lymphomas have an indolent natural course and are slow to disseminate. Recurrences, that can occur after many years, may involve other extranodal sites and occur more often in patients with extragastric MALT lymphomas than in patients with primary gastric disease (Raderer et al., 2005). The tumors are sensitive to radiation therapy, and local treatment may be followed by prolonged disease-free intervals. Involvement of multiple extranodal sites and even BM involvement do not appear to confer a worse prognosis (Thieblemont et al., 2000). Protracted remissions may be included in H. pylori-associated gastric MALT lymphoma by antibiotic therapy for H. pylori (Neubauer et al., 1997, Wotherspoon et al., 1993). Cases with the t(14;18)(q21;q21) appear to be resistant to H. pylori eradication therapy (Liu et al., 2001). In IPSID, remissions have followed therapy with broad-spectrum antibiotics (Ben Ayed et al., 1989, Lecuit et al., 2004). Antibiotics have also been used to successfully treat selected other MALT lymphomas. Transformation to diffuse large B-cell lymphoma may occur.

2. Regression of rectal MALT lymphoma after antibiotic treatments

2.1 Introduction

MALT lymphoma is less frequently seen in the rectum(Isaacson, 1999b, Morton et al., 1993, Koch et al., 2001), while the presence of *MALT1* gene translocation in rectal MALT lymphoma has occasionally been reported (Motegi et al., 2000, Remstein et al., 2000, Yonezumi et al., 2001). In addition, a few reports have described the regression of rectal MALT lymphomas after antibiotic treatments that are generally found to be successful for gastric MALT lymphomas(Raderer et al., 2000, Matsumoto et al., 1997).

In addition to *H. pylori*, various other infectious agents have been reported to be related to the development of MALT lymphoma, such as *Borrelia burgdorferi* in cutaneous(Roggero et al., 2000), *Chlamydia psittaci* in orbital(Ferreri et al., 2004), and *Campylobacter jejuni* in small intestinal lymphoma(Al-Saleem & Al-Mondhiry, 2005). However, few data are available on the pathogenesis of MALT lymphoma of organs other than the stomach.

In this study, we examined 8 rectal MALT lymphomas to determine whether they regressed after antibiotic treatments. We report here our findings and also discuss the relationship between rectal MALT lymphomas and *MALT1* gene genetic abnormalities (Niino et al., 2010).

2.2 Materials and methods

2.2.1 Rectal MALT lymphoma cases

Formalin-fixed, paraffin-embedded tissues obtained between 2004 and 2007 from 8 cases of rectal MALT lymphoma treated with antibiotic treatments were retrieved from the pathology files at Kurume University School. The patients consisted of 2 men and 6 women, ranging in age from 41 to 80 years (median, 66 years). Lymphomas constituting secondary involvement of the rectum were not included in the study. Clinical data for all cases were obtained from pathological reports and medical reports, and all cases were reviewed to confirm that the histological diagnosis conformed to the criteria of the World Health Organization Classification for Tumors of Hematopoietic and Lymphoid Tissues

(Swerdlow et al., 2008). Diagnosis of rectal MALT lymphomas was based on the following findings: centrocyte-like cells and/or monocytoid cell proliferation, especially at the outside of the mantle zone (marginal zone distribution); presence of plasmacytic differentiation and/or follicular colonization in some cases; and absence of CD5, CD10, and cyclin D1 overexpression. Lymphoepithelial lesions in rectal MALT lymphomas were not as obvious as those in gastric tumors (representative histologies are shown in Fig. 1.). All patients were Japanese. *H. pylori* infection was assessed by rapid- urease test or histological examination.

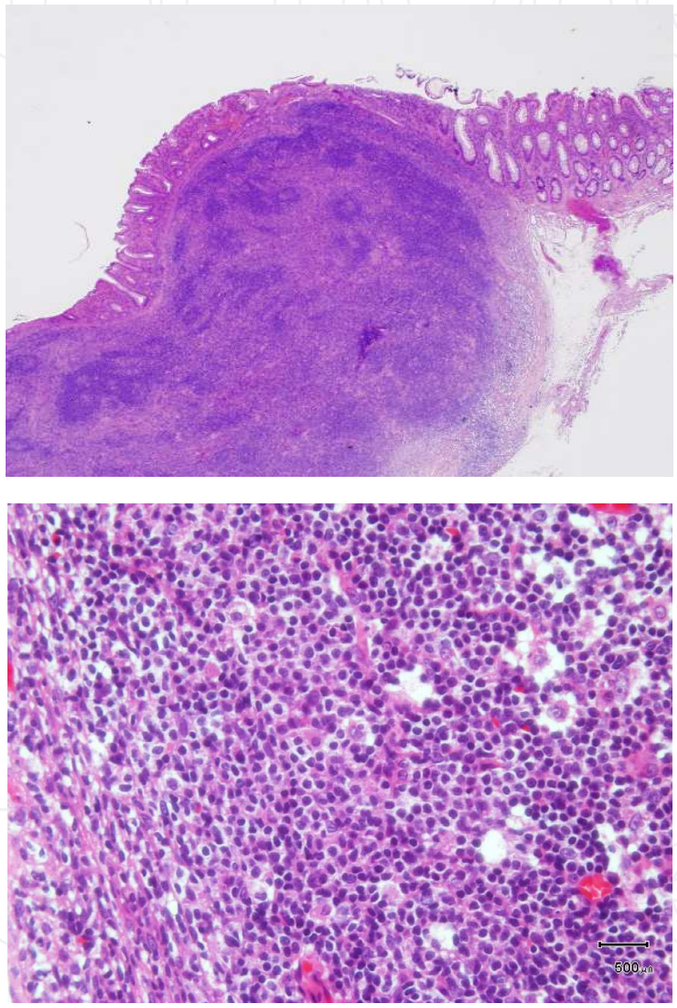

Fig. 1. Hematoxylin and eosin staining show the histopathologic features of rectal mucosa-associated lymphoid tissue (MALT) lymphoma. (A) Dense, diffuse atypical lymphocyte infiltration, mainly in submucosal layer. (B) MALT lymphoma cells showing small nuclei and abundant pale staining cytoplasm, resulting in a monocytoid appearance. (Niino et al., 2010)

Because Inoue and Chiba reported a case without infection of *H. pylori* whose rectal MALT lymphoma regressed after administration of antibiotics(Inoue & Chiba, 1999), the patients were treated with antibiotic treatments. After informed consent had been obtained, 8 patients underwent antibiotic treatments with a combination of antibiotics (clarithromycin

and amoxicillin), and follow-up endoscopic examinations including biopsies were performed. Tumor regression after antibiotic treatments was histologically evaluated. Complete regression (CR) was defined as the total disappearance of lymphoma and absence of histopathological evidence of lymphoma on endoscopic biopsy. No regression (NR) was diagnosed when no macroscopic or histologic changes were present. This study was carried out in accordance with the Helsinki Declaration as revised in 1989 and with the ethical guidelines of the participating centers and countries.

2.2.2 Polymerase Chain Reaction (PCR) for the detection of IgH rearrangements

DNA was extracted from 5-μm-thich sections of a paraffin block. Gene amplification of the IgH gene from the framework 2 part of the V segment to the J region by a seminested PCR was performed by using the consensus primers complementary to the framework 2 portion of the VH region (FR2B) and the JH region (CFW1) from genomic DNA. The following primer sequences were used: FR2B, 5′-GTCCTGCAGGC(C/T)(C/T) CC-GG(A/G)AA(A/G)(A/G)GTCTGGAGTGG-3′; CFW1, 5′-ACCTGAGGAGACGGT-GACCAGGGT-3′. The PCR conditions were as follows: after initial denaturation at 95°C for 10 min, 5 cycles (95°C for 30 s, 63°C for 30 s and 72°C for 30 s) followed by 45 cycles (95°C for 30 s, 60°C for 30 s and 72°C for 30 s) with a final extension at 72°C for 10 min. The size of the IgH rearrangement fragments was usually between 250 and 300 bp.

2.2.3 *MALT 1* gene translocation analysis

All cases were analyzed using a *MALT1* break-apart probe (Vysis, Downer's Grove, IL, USA). Interphase fluorescence in situ hybridization (FISH) studies were performed on intact 5-μm sections of formalin-fixed, paraffin-embedded material as previously described in detail(Wongchaowart et al., 2006). Briefly, slides were baked overnight at 60°C, deparaffinized, and subjected to proteinase K treatment. After washing, 10 mL of the probe solution was applied, and probe and target DNA were allowed to codenature at 73°C for 5 minutes and to hybridize overnight at 3°C. Slides were counterstained with DAPI, and signals were visualized on an Axioskop photomicroscope (Zeiss, Oberkochen, Germany). For each probe 100-200 nuclei were scored. Nuclei were considered to be positive for a break-apart probe when a nucleus contained separate red and green signals at least three signal widths apart. Nuclei were scored as positive for +*MALT1* when three or more signals were identified within one nucleus. Cutoffs for interpretation as a positive result were determined for each abnormality based on the analysis of six formalin-fixed, paraffin-embedded sections of benign lymph nodes and tonsils used as control. Cutoff thresholds for each abnormality were established as the mean plus three standard deviations of the mean, so that positivity for *MALT1* translocation, or +*MALT1*, was defined as >4% nuclei with a positive signal pattern.

2.3 Results

2.3.1 Clinical features of rectal MALT lymphoma

Clinical characteristics of this study are shown in Table 1. The clinical records of all cases showed rectal origin. Four of eight patients (50%) were positive and one patient (13%) was

negative for *H. pylori*. The remaining patients were not evaluated for *H. pylori*. Five cases occurred as a single tumor, whereas the remaining three cases occurred as multiple tumors. Elevated lesions (polypoid or flat elevation) were formed in 7 cases, whereas circumferential lesion was formed in one case (Case 4). Representative endoscopic image before antibiotic treatment demonstrated multiple small polyps (Case 2) (Fig. 2.). The size of MALT lymphoma ranged from 5 to 100 mm. Seven cases were localized in the submucosa, whereas one case (Case 4) involved the subserosa.

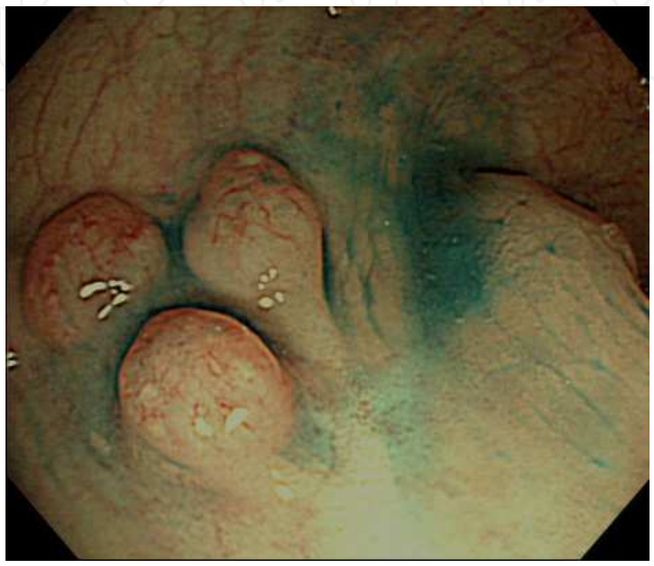

Fig. 2. Representative endoscopic image before antibiotic treatment (Case 2): Colonoscopy demonstrated multiple small polyps. (Niino et al., 2010)

Case no.	Age (y)	Sex	Number	Shape	Size (mm)	Depth	LDH (IU/l)	IL2R (U/ml)	*H.pylori* status
1	67	F	multiple	polypoid	5-10	SM	178	888	positive
2	68	F	single	flat elevation	25	SM	192	NA	positive
3	76	F	single	polypoid	10	SM	NA	NA	NA
4	65	M	single	circumferential	100	SS	NA	NA	NA
5	41	M	multiple	flat elevation	10	SM	215	530	negative
6	80	F	single	polypoid	20	SM	160	369	positive
7	54	F	single	polypoid	15	SM	156	NA	positive
8	46	F	multiple	polypoid	5-7	SM	NA	NA	NA

Abbreviations: LDH, lactate dehydrogenase; IL2R, interleukin 2 receptor; SM, submucosa; *H.pylori, Helicobacter pyroli*; SS, subserosa; NA, not available

Table 1. Clinical characteristics of rectal MALT lymphoma. (Niino et al., 2010)

2.3.2 Detection of IgH rearrangements and *MALT1* gene translocation

PCR for the detection of IgH rearrangement resulted in the identification of a monoclonal band in 7 cases (87.5%) (Table 2).

Results of interphase FISH studies are shown in Table 2 and Fig.3. All cases were successfully analyzed for *MALT1* translocation by FISH. One case demonstrated *MALT 1* gene translocation (one fusion, one orange, and one green signal pattern), while another case demonstrated partial deletion of the *MALT1* gene (one fusion and one green signal pattern). The others showed the normal pattern (two fusion signal patterns). That is, two cases (25%) showed genetic abnormality.

Case no.	PCR-IgH	MALT1 FISH	Response
1	Monoclonal	Negative	CR
2	Monoclonal	Negative	CR
3	Monoclonal	Negative	CR
4	Monoclonal	Partial deletion	NR
5	Monoclonal	Negative	NR
6	Polyclonal	Negative	CR
7	Monoclonal	Rearrangement	NR
8	Monoclonal	Negative	CR

Abbreviations: PCR, polymerase chain reaction;
IgH, immunoglobulin heavy chain;
MALT, mucosa associated lymphoid tissue;
FISH, fluorescence in situ hybridization;
CR, complete regression; NR, no regression.

Table 2. Results and clinical outcomes. (Niino et al., 2010)

2.3.3 Therapeutic outcomes

Therapeutic outcomes are shown in Table 2, 3. Eight patients who had undergone antibiotic treatments were subjected to follow-up colonoscopy after the treatment. Five patients (62.5%) achieved CR after a median follow-up from antibiotic treatments of 5 months (range, 3 to 58 months). Three patients (37.5%) showed NR, among which received further treatment, including chemotherapy. These findings strongly indicate that these cases of rectal MALT lymphoma were responsive to antibiotic treatments. None of the patients who responded to antibiotic treatments harbored *MALT1* gene genetic abnormality, but it was detected in two of the three patients who did not respond. The cases with *MALT1* gene genetic abnormality thus tended to be resistant to antibiotic treatments.

	Antibiotic treatments sensitive cases	Antibiotic treatments resistant cases	Total
Genetic abnormality (+)	0	2	2
Genetic abnormality (-)	5	1	6
Total	5	3	8

Table 3. Relationship between antibiotic treatments sensitivity and *MALT1* gene genetic abnormality. (Niino et al., 2010)

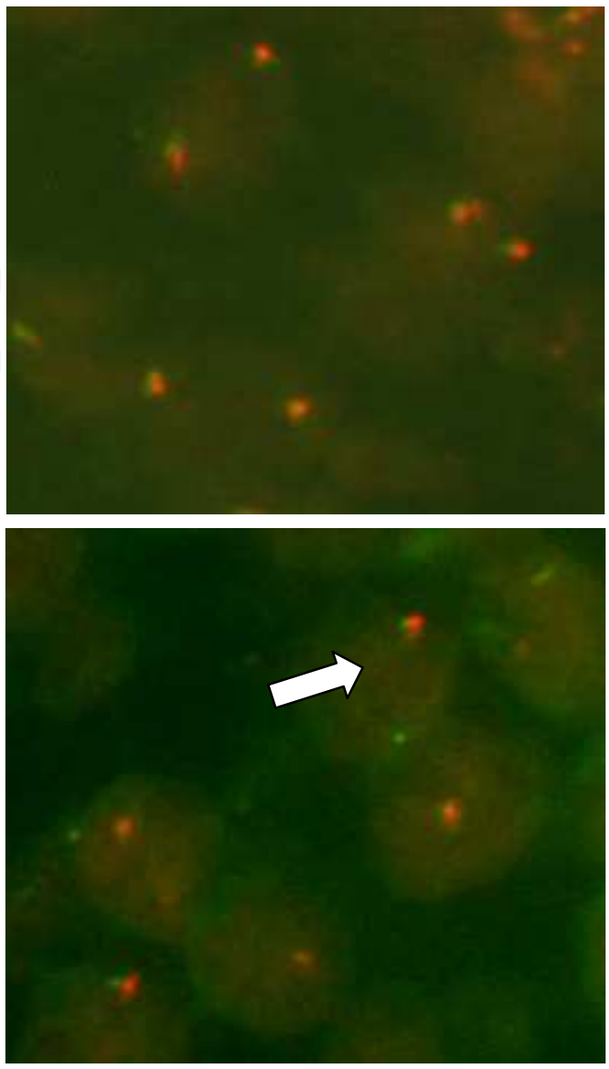

Fig. 3. Interphase fluorescence in situ hybridization (FISH) patterns in representative cases. (A) Normal pattern (two fusion signal patterns). (B) Partial deletion of *MALT1* gene (one fusion and one green signal pattern; arrows). (Niino et al., 2010)

2.4 Discussion

Gastric MALT lymphoma is often associated with infection by *H. pylori*. Eradication of *H. pylori* has therefore been investigated as the first line of treatment for patients with MALT lymphoma of the stomach, and has been found to be highly effective for patients with localized low-grade disease. On the other hand, regression of rectal MALT lymphoma after antibiotic treatments has also been reported. Matsumoto *et al.* reported the first case with rectal MALT lymphoma that regressed after antibiotic treatment in 1997 (Matsumoto et al., 1997). They also stated that the association of MALT lymphoma with *H. pylori* is not limited to the stomach, but involves other organs in which MALT is the predominant tissue for host defense. Inoue and Chiba reported a case without infection of *H. pylori* whose rectal MALT lymphoma regressed after administration of antibiotics(Inoue & Chiba, 1999). Nakase *et al.*

reported three *H. pylori*-negative cases of rectal MALT lymphoma which regressed after antibiotic treatments(Nakase et al., 2002). Regression of rectal MALT lymphoma after administration of quinolones has also been reported (Ferreri et al., 2005). These results suggest that some antigenic stimuli other than *H. pylori* may play a role in the pathogenesis of MALT lymphoma of the rectum, which is constantly exposed to intestinal bacteria and contents. However, for the time being this must remain an unproven hypothesis.

Recently, the *t*(11;18) chromosomal translocation was identified as a specific chromosomal abnormality in some MALT lymphomas, and the *API2-MALT1* fusion gene was found to be associated with this abnormality(Yonezumi et al., 2001). The *MALT1* gene is cloned by 18q21, while *API2*, an apoptosis inhibitor, is present in 11q21. Yonezumi et al. used RT-PCR to test a large series of MALT lymphomas for the presence of the *AP12-MALT1* fusion gene and found that pulmonary MALT lymphomas showed the highest incidence of the *AP12-MALT1* gene (62.5%) while the occurrence rates of MALT lymphomas of the stomach, orbit and large intestine ranged from 10 to 20%(Yonezumi et al., 2001). Sakugawa et al. used RT-PCR to examine 47 colorectal MALT lymphomas, including 27 primary rectal MALT lymphomas, for the *API2-MALT1* fusion gene. *API2-MALT1* fusion gene positivity was observed in 3 (11%) of 27 cases of rectal MALT lymphoma, and in 7 (15%) of 47 cases of colorectal MALT lymphoma(Sakugawa et al., 2003). In our study, the positive ratio for *MALT1* gene genetic abnormality was 2 (25%) of 8 cases of rectal MALT lymphoma. In addition, we found that rectal MALT lymphomas with *MALT1* gene genetic abnormality tend to be resistant for antibiotic treatments.

3. Conclusion

Ours is the first investigation of the regression of rectal MALT lymphoma after antibiotic treatments (Niino et al., 2010). Further follow-up will be needed to determine whether MALT lymphoma of the rectum regresses completely or is actually cured by antibiotic treatments. In addition, a large number of such cases needs to be analyzed to establish suitable standards for antibiotic treatments.

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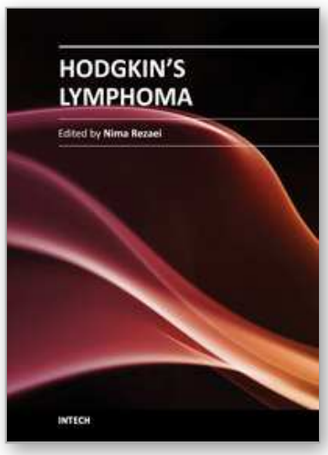

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Hodgkin's Lymphoma is the book consisting of 11 chapters: Recent insights into the biology of Hodgkin's lymphoma, including historical aspects, epidemiology, pathophysiology, genetic defects, and prognostic indicators are explained in the intro chapters. After a translational chapter from tumor microenvironment to immunotherapeutic approach, treatment of early stage, advanced, and refractory Hodgkin's lymphoma are explained in the following chapters. MALT lymphoma and adverse effects of chemotherapy and radiotherapy in the affected patients are discussed in the subsequent chapters, while the final chapter is focused on survivorship in Hodgkin's lymphoma. The book is intended to present recent advances in the pathophysiology of Hodgkin's lymphoma as well as practical approach to diagnosis and management in clinical practice, which is hoped to be welcomed by the physicians, who wish to learn more about Hodgkin's lymphoma.

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