

Helicobacter pylori Eradication Therapy for Colorectal Mucosa-associated Lymphoid Tissue Lymphoma: Report of Two Cases

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Two cases of colorectal mucosa-associated lymphoid tissue lymphoma (cMALT) are presented and discussed with the reports from 1997 to the present. *Helicobacter pylori* (HP)-negative cases showed tumor resolution 2 months after eradication therapy. HP-positive cases were successfully eradicated and tumor resolution was confirmed 16 months later. Analysis of the data reported to date shows that cMALT resolution rates were 68.4% (13/19) in the HP-negative group and 33.3% (7/21) in the HP-positive group. HP eradication should be considered the primary treatment for cMALT regardless of HP infection, especially in untreated patients under follow-up.

Key words: colorectal MALT lymphoma, *H. pylori* eradication, antibiotics, *H. pylori*-negative

INTRODUCTION

Treatment of colorectal MALT lymphoma (cMALT) generally consists of surgical resection, radiation therapy, chemotherapy, or follow-up with no treatment, and *Helicobacter pylori* (HP) eradication therapy has been considered, but no clear guidelines for it have been provided. Matsumoto *et al.* reported in 1997 that HP-positive cMALT showed regression after eradication of HP [1], and Inoue *et al.* reported in 1999 that HP-negative cMALT showed regression after eradication of HP [2]. Since then, there has been a series of reports on cMALT and HP eradication therapy in Japan. In this article, a case of HP-positive and one of HP-negative cMALT lymphoma at our institution are described, along with a literature review of the case reports from 1997 to the present.

CASE REPORT

Case 1

A 67-year-old woman underwent upper and lower gastrointestinal endoscopies to investigate mild anemia (hemoglobin 10.9 g/dl), and colonoscopy (CS) showed a 30-mm granular raised lesion in the ascending colon (Fig. 1a). Magnified narrow band imaging (NBI) showed dilated vessels on the mucosal surface (Fig. 1b), but chromoendoscopy showed a type I pit pattern (Fig. 1c). Endoscopic ultrasonography (EUS) showed the lesion as a second layer of wall thickening (Fig. 1d). Histopathological examination of a biopsy specimen taken from the lesion site showed MALT lymphoma (Fig. 2a-f), and EBER was negative. HP infection was evaluated by urinary antibody, stool antigen, and urea breath tests, all of which were negative, and gastrointestinal endoscopy (GIE) showed no gastric MALT

lymphoma or atrophic changes in the gastric mucosa. Abdominal ultrasonography, contrast-enhanced magnetic resonance imaging (MRI), and positron emission tomography-computed tomography (PET-CT) showed no neoplastic lesions elsewhere, including surrounding lymph nodes, leading to a diagnosis of HP-negative, primary colonic MALT lymphoma. After discussion with the patient and consultation with the hematology/oncology department, minimally invasive HP eradication therapy (vonoprazan 20 mg, amoxicillin 750 mg, clarithromycin 200 mg twice daily for 7 days; VAC) was performed as the primary treatment for cMALT. On CS performed two months after the eradication therapy, the tumor had disappeared (Fig. 3a, b), and biopsy results showed no tumor cells. The patient is currently under outpatient observation.

Case 2

A 69-year-old woman with a positive fecal occult blood test underwent GIE and CS. GIE showed atrophic gastritis, and biopsy tissue and blood antibodies were positive for HP. The initial CS findings were two submucosal tumor-like bumps, 7–8 mm in size (Fig. 4a, b), and EUS showed a second layer of wall thickening (Fig. 4c) and there was no evidence of proximal lymphadenopathy. Biopsy histology of the same lesion confirmed MALT lymphoma, and HP eradication therapy (VAC) was performed as Stage I. The urea breath test was negative, and after 3 months of HP eradication therapy, the tumor showed a shrinking trend (Fig. 5a); after 11 months, the tumor flattened (Fig. 5b), but the tumor remained in the biopsy tissue. Sixteen months later, the tumor had disappeared (Fig. 5c), and the biopsy result was also negative. There has been no recurrence since then, even after 5 years.

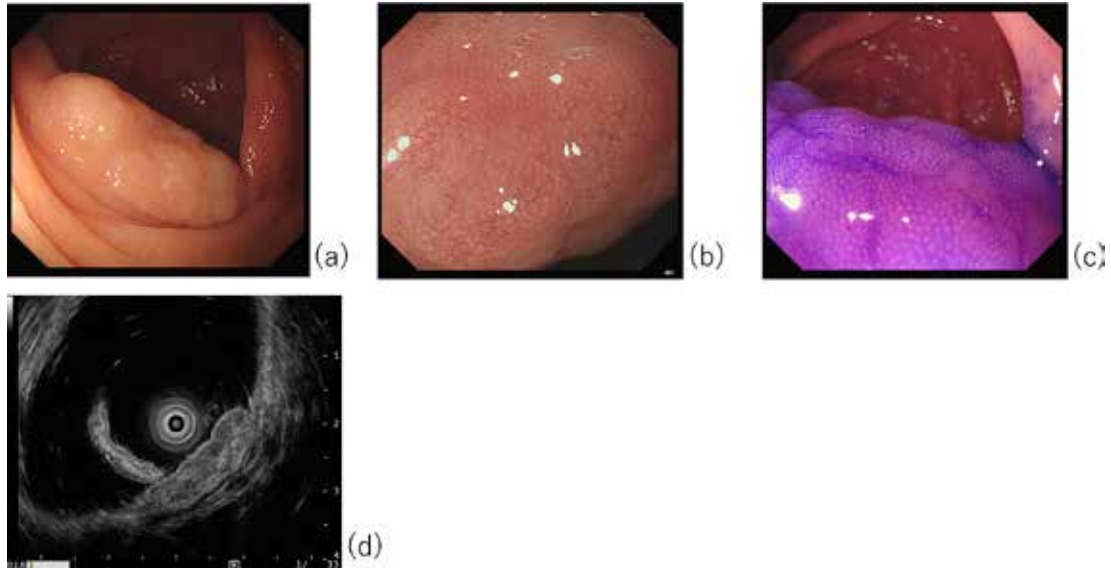


Fig. 1 (a) A large, 30-mm, granular elevated lesion in the ascending colon. (b) Narrow band imaging (NBI) with magnification shows vascular hyperplasia on the mucosal surface. (c) Chromoendoscopic examination shows a normal type I pit pattern on the surface. (d) EUS shows a thickened second layer.

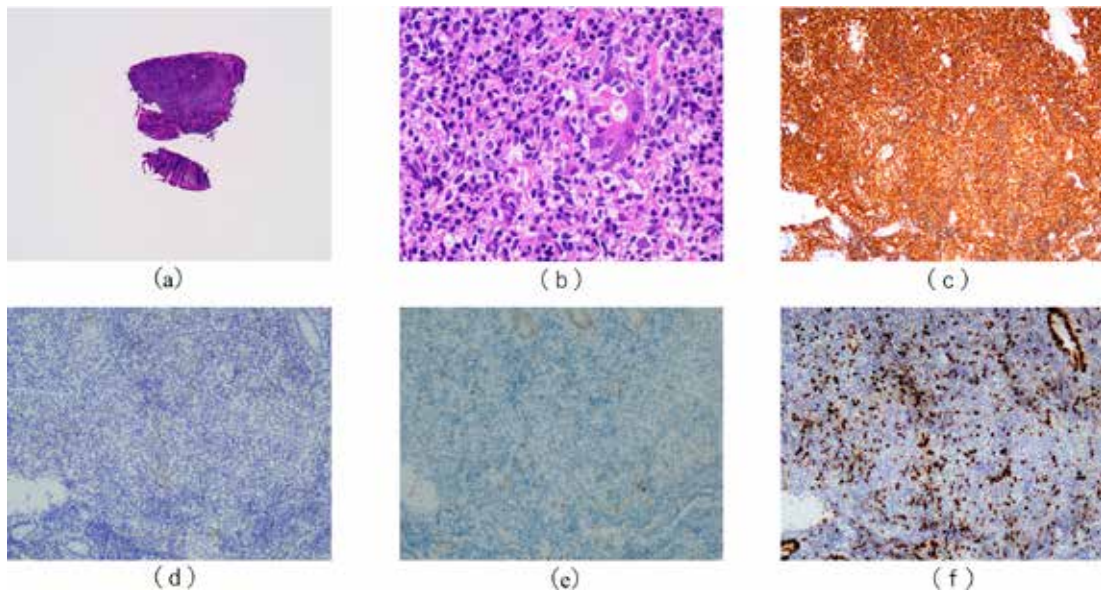


Fig. 2 (a) HE staining shows diffuse, dimly nodular proliferation of medium-sized lymphocytes with pale cytoplasm in the mucosal intrinsic layer. (b) Strongly magnified image (400x), monocytoid B-cell proliferation and lymphoepithelial lesion. (c) Positive for CD20 immunostaining. (d) Negative for CD10 immunostaining. (e) Negative for CyclinD1 immunostaining. (f) MIB1 Index: 10%.

DISCUSSION

Marginal zone lymphoma (MZL) is a non-Hodgkin's lymphoma that starts with B lymphocytes; MZL involves lymph nodes, spleen, and mucosa-associated lymphoid tissue (MALT) [3]. Extranodal MZL is reported to account for 67% of all MZLs, and by organ, the gastrointestinal tract accounts for a large proportion of extranodal MZLs (38%), with the stomach being the most common (80%), followed by the large intestine (12%) and small intestine (8%) [4]. The first-line treatment for gastric MALT lymphoma in

localized stages is *HP* eradication therapy [5, 6]. In a Japanese, multicenter, cohort, follow-up study, gastric MALT lymphoma with successful eradication of *HP* had a good prognosis, with a relapse rate of 3.1%, and when *HP* eradication failed, chemotherapy, surgical resection, chemoradiation, antibiotic therapy, rituximab monotherapy, and endoscopic resection were used as secondary therapy, and all of them had good outcomes [7]. Recently, it has been reported that *HP*-negative gastric MALT lymphoma is increasing and tends to affect younger patients than *HP*-infected gastric MALT lymphoma [8], and it has been found that 27.9% of

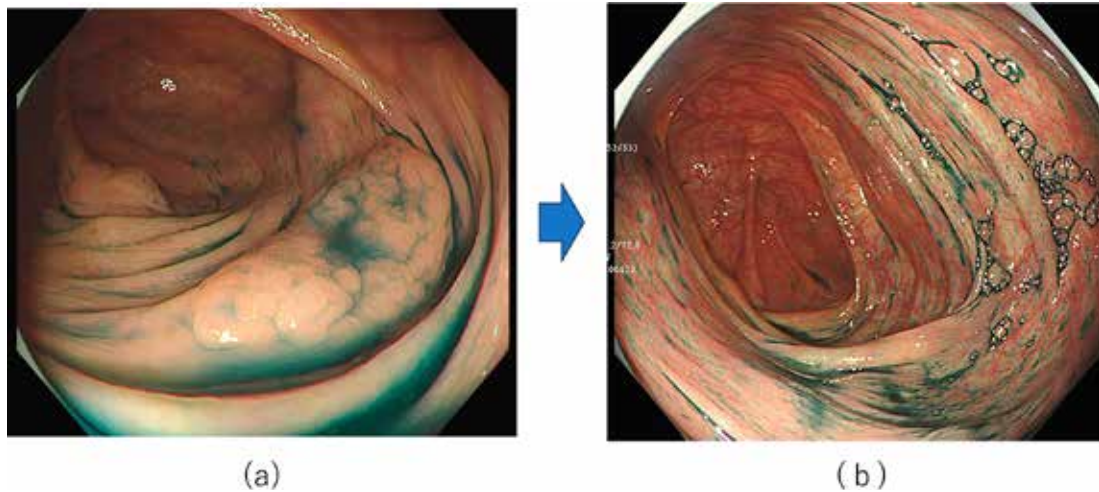


Fig. 3 (a) Pre-treatment endoscopic findings.
(b) Endoscopic findings after treatment.

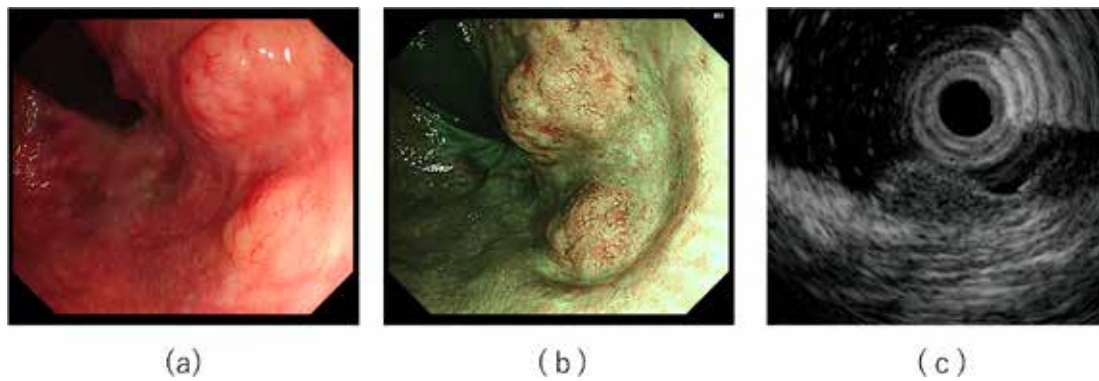


Fig. 4 (a) Two submucosal tumor-like bumps, 7-8 mm in size.
(b) Narrow band imaging (NBI) with magnification shows dendritic vascular hyperplasia on the mucosal surface.
(c) EUS shows a thickened second layer.

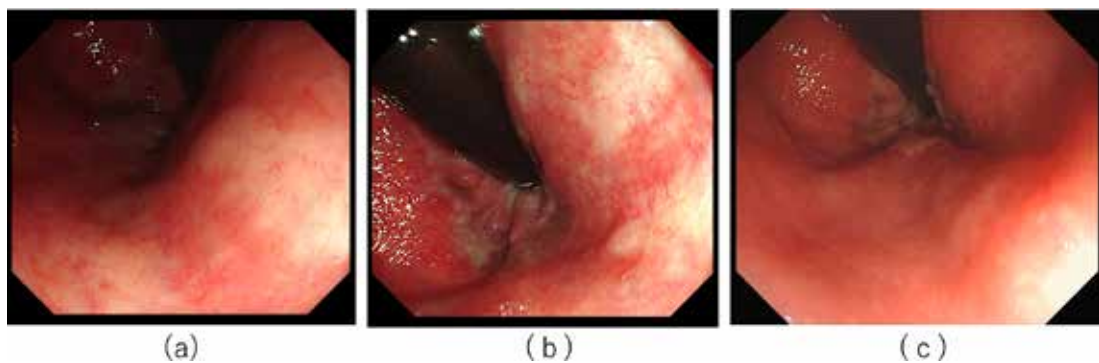


Fig. 5 (a) Tumor tends to shrink after 3 months of sterilization treatment.
(b) Flattening of tumor after 11 months.
(c) Disappearance of tumor after 16 months.

HP-negative patients can achieve remission with eradication therapy [9], but no consensus opinion has been reached.

Unlike gastric MALT lymphoma, cMALT lymphoma occurs less frequently, and no clear treatment strategy is currently available. According to the algorithm proposed by the Japanese Society of Hematology [10], the treatment strategy for non-gastric MALT lymphoma is surgical resection, radiation therapy,

or no treatment at stage I. In this study, data on 40 patients (excluding those with unknown *HP* infection), including our own patients, who were treated with *HP* eradication therapy or antibiotics were analyzed by searching the Central Journal of Medicine and MEDLINE (1997-present) using the key words “colon” or “rectum” and “MALT lymphoma” (Table 1) [1, 2, 11-43]. The mean age of the patients was 64.2 years, the male to female ratio was 13:27, the *HP* infection

Table 1 Summary of reported cases

Case	Reporter	Reporting year	Age	Sex	Position	Number of lesions	Depth	<i>HP</i> infection	Medication*	Effect
1	Matsumoto	1997	72	F	R	1	mp	+	PAC	disappear
2	Inoue	1999	62	F	R	1	sm	-	PAC	disappear
3	Raderer	2000	67	M	D	1	ND	+	PCM	disappear
4	Inoue	2001	67	M	R	1	sm	+	PAC	disappear
5	Nakase	2002	66	F	D/R	multiple	sm	-	PAMT	disappear
6	Nakase	2002	33	F	R	1	ND	-	AC	disappear
7	Hisabe	2002	70	F	R	1	mp	-	PAC	disappear
8	Oiya	2003	54	F	R	1	sm	-	PAC	disappear
9	Kagami	2003	52	F	R	1	ND	-	PAC	disappear
10	Hori	2004	83	F	R	1	ss	+	PAC→PAM→G	disappear
11	Dohden	2004	60	F	R	1	mp	+	L	disappear
12	Sasaki	2004	64	M	D/S	2	sm	+	PAC	increase
13	Kikuchi	2005	80	F	C/R	multiple	sm	-	PAC	reduction
14	Kikuchi	2005	71	M	R	multiple	se	-	AC	disappear
15	Arakura	2005	63	M	R	multiple	sm	-	PAC	other lesions
16	Hisabe	2006	69	F	R	2	sm	+	PAC	reduction
17	Hisabe	2006	75	M	R	2	sm	+	PAC	reduction
18	Mimura	2006	68	M	A	1	sm	+	PAC	disappear
19	Shirakawa	2006	56	F	R	2	sm	-	L	No change
20	Adachi	2006	61	F	total colon	multiple	sm	+	PACM	No change
21	Matsuo	2006	75	F	T	1	mp	+	PAC	increase
22	Takabayashi	2008	75	F	S	1	ND	-	ND	No change
23	Yamamoto	2008	69	F	R	multiple	ND	+	PAC	increase
24	Amouri	2009	46	F	R	1	ND	+	PAM	No change
25	Nomura	2010	53	F	R	1	sm	-	PAC	disappear
26	Onizuka	2011	61	M	S	1	ND	+	PAC	No change
27	Yamamoto	2011	33	F	R	1	ND	+	PAC→PAM	increase
28	Ohara	2012	53	M	R	multiple	ND	-	PAC	disappear
29	Yasuda	2013	71	M	S	1	ND	+	PAC	No change
30	Ohana	2013	31	F	R	multiple	ND	-	PAC→PAM	No change
31	Naito	2014	64	F	R	1	ND	+	PAC→L→AM	No change
32	Ueda	2014	67	F	T	multiple	ND	-	PAC	increase
33	Onji	2015	80	F	R	2	MP	+	PAC	No change
34	Sahara	2015	85	M	S	1→multiple	ND	+	PAC	increase
35	Ito	2018	78	F	R	1	sm	-	PAC	disappear
36	Matsumoto	2019	56	F	R	1	ND	-	PAC	disappear
37	Mitsuyama	2020	81	M	C	1	ND	-	PAC	disappear
38	Kusano	2021	60	M	R	1	sm	+	PAC	increase
39	Our case	2023	67	F	A	1	sm	-	PAC	disappear
40	Our case	2023	69	F	R	1	sm	+	PAC	disappear

* P: proton pump inhibitor, A: amoxicillin, M: metronidazole, T: tetracycline, G: gatifloxacin, L: levofloxacin, ND: none noted

rate was 52.5% (21/40), and the most common site of involvement was the rectum, although there was some overlap within the colon. Endoscopic findings were more often of the polypoid type, which lacked epithelial changes on the mucosal surface and presented sub-mucosal tumor-like findings (Table 2). A comparison of *HP* infection and cMALT disappearance rates after antimicrobial therapy, including *HP* eradication therapy, was performed, and the *HP*-negative group tended to have a higher rate, at 68.4% (13/19), compared with 33.3% (7/21) in the positive group (Table 3). In the two cases in the present study, there was an opinion favoring follow-up, but after consultation with the patients and the hematology/oncology department, *HP* eradication treatment was selected as the primary therapy. In case 1 (*HP*-positive), the tumor gradually shrank and disappeared after successful *HP* eradication, but in case 2 (*HP*-negative), the tumor disappeared after 2 months of *HP* eradication treatment, suggesting that the association between cMALT and *HP* infection is

unclear. The reason for the disappearance of cMALT could be changes in the intestinal microbiota caused by antibiotics [44] or acid secretion inhibitors [45] with or without *HP* infection, but case 1 could also be due to immune changes because of the disappearance of chronic persistent *HP* infection. Although immune alterations due to infection with non-*Helicobacter pylori Helicobacter* (*NHPH*; *H. heilmannii*, *H. suis*, *H. bizzozeronii*, etc.) are possible in both cases [46], MALT lymphoma occurs in all organs, and chronic infection or chronic dysregulation of NF- κ B activity due to chronic inflammatory and immune responses, as well as genetic abnormalities and chromosomal translocations, was also considered [47]. In recent reports on the treatment of localized cMALT, *HP* eradication therapy has been seen in scattered cases in Japan, but there are many overseas reports of endoscopic resection cases [48, 49], and this may be an option for primary treatment in the future. It has been reported that antibiotic therapy is not effective for *HP*-infected patients with extra-

Table 2 Summary of cMALT patients

Age average	64.2
Male:Female	13:27
<i>H. pylori</i> infection	positive 21 negaitive 19
Position (Including duplicate cases)	Rectum 28 Sigmoid colon 5 Descending colon 3 Transverse colon 2 Ascending colon 2 Cecum 2 total colon 1
Number of lesions(Including duplicate cases)	one lesion 28 two lesions 5 multiple lesions 11
Endoscopic findings	polypoid type 36 ulcerative type 3 MLP* type 3 diffuse-infiltrating type 2

*MLP: multiple lymphomatous polyposis

Table 3 cMALT changes after eradication therapy in *H. pylori* positive and negative groups

	cMALT disappearance	cMALT residual
<i>HP</i> (+) group (n = 21)	7(33.3%)	14
<i>HP</i> (-) group (n = 19)	13(68.4%)	6

gastric MALT lymphoma, among whom 4 cMALT cases were HP-positive and 2 were HP-negative [50]. The results of all cMALT cases we searched in this study and those reported with HP eradication therapy showed resolution of lesions with or without HP infection. Although some suggested that the patient should be followed up, after consultation with the patient and the hematology/oncology department, HP eradication therapy was selected as the primary treatment.

In conclusion, the present cases of HP eradication therapy in HP-positive and HP-negative cMALT cases, in which tumor regression was observed in both cases, suggest that HP eradication therapy (especially in untreated, follow-up cases) is a less invasive option for the first-line treatment of cMALT.

ACKNOWLEDGMENTS

Ethics Declaration

Conflict of Interest

The authors declare that they have no conflicts of interest.

Human and animal rights

All procedures were carried out in accordance with the ethical standards of the 1964 Declaration of Helsinki and its subsequent amendments.

Informed Consent

No patient-identifying information was included in this study.

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