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Case report

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Deep infiltrative low-grade MALT (mucosal-associated lymphoid tissue) colonic lymphomas that regressed as a result of antibiotic administration: endoscopic ultrasound evaluation

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Since 1997 we have experienced three cases of low-grade colonic mucosal-associated lymphoid tissue (MALT) lymphomas. The depth of tumor invasion was evaluated by endoscopic ultrasonography (EUS) and the mass lesions were all diagnosed as having extended beyond the deep region of the submucosal layer. Although all of these patients tested negative for gastric *Helicobacter pylori*, their tumor lesions regressed after antibiotic treatment in accordance with *H. pylori* eradication therapy. In general, consensus has been reached regarding antibiotic therapy for gastric MALT lymphomas. However, as a prerequisite for antibiotic therapy, the therapy has been deemed effective against these gastric tumors if the extent of infiltration, as evaluated by EUS, is limited to the mucosal layer or the superficial region of the submucosal layer. Based on the therapeutic outcomes seen in the three patients studied here, it is suggested that antibiotic therapy might be useful in treating MALT lymphomas of the colon, even in patients with advanced invasive tumors, in contrast to the extent of the lesions in the stomach suitable for antibiotic treatment. The success of the antibiotic treatment also suggests that MALT lymphomas may be caused by unknown luminal microorganisms, other than *H. pylori.*

Key words: colonic MALT lymphoma, *Helicobacter pylori*, antibiotic therapy, endoscopic ultrasound

Introduction

The efficacy of antibiotic therapy in treating colonic mucosal-associated lymphoid tissue (MALT) lymphomas has become increasingly definite,[1–7] although it is not yet well-documented. In contrast to gastric MALT lymphomas, in which the depth of invasion that can be effectively treated with antibiotic therapy is known, the depth of invasion of colonic MALT lymphomas suitable for such treatment remains unresolved. In this report, we document the results of our study of patients with MALT lymphomas who underwent endoscopic ultrasonography (EUS) prior to antibiotic therapy.

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Case 1

In October 2000, a health examination revealed a positive fecal occult blood test in a 71-year-old man. Colonoscopic examination revealed a nodular protruding mass lesion, measuring 35 mm, covered with normal mucosa, on the surface (Fig. 1a), and small protruding and small excavated lesions in the surrounding area. Biopsy specimens disclosed the diffusely infiltrated proliferation of medium-sized atypical lymphocytes with round or irregular nuclei in all specimens. Immunostaining results were CD20 (+), CD45RO (–), CD10 (–), bcl-2 (–), and CD5 (–); based on these findings, the mass lesion was diagnosed as a low-grade MALT lymphoma. On EUS, the primary lesion was seen to have penetrated extramurally (Fig. 1b).

On chest radiography, abdominal computed tomography (CT) scans, and gallium scintigraphy, neither swelling of lymph nodes nor any infiltration into other organs was revealed, and thus a diagnosis of stage IE was made. Furthermore, a bone-marrow puncture led to the diagnosis of myelodysplastic syndrome, and anemia, and showed a decreased platelet count, findings which were considered to be the result of the disease. An upper gastrointestinal endoscopic examination yielded no abnormal findings. Negative test results for *Helicobacter pylori* were confirmed by cultures, by macroscopic examination of specimens, and by serum

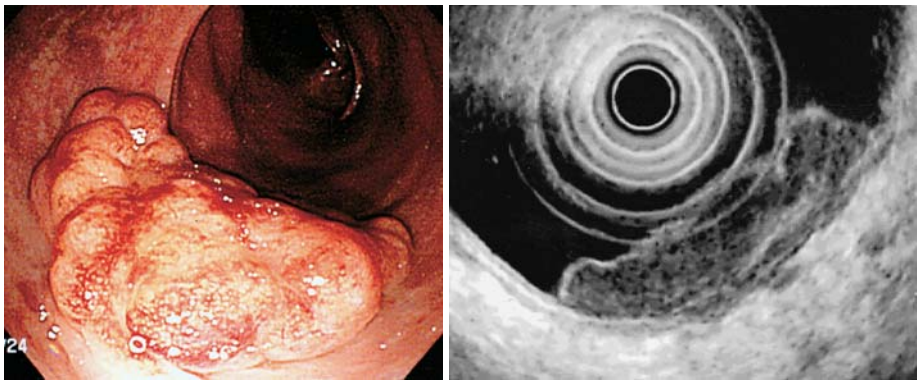

Fig. 1. a Endoscopic findings in case 1. Before antibiotic therapy, a sessile tumor, 4 cm in size, without ulceration, was observed in the rectum. **b** Endoscopic ultrasonography in case 1, showing a large extramurally infiltrating mass

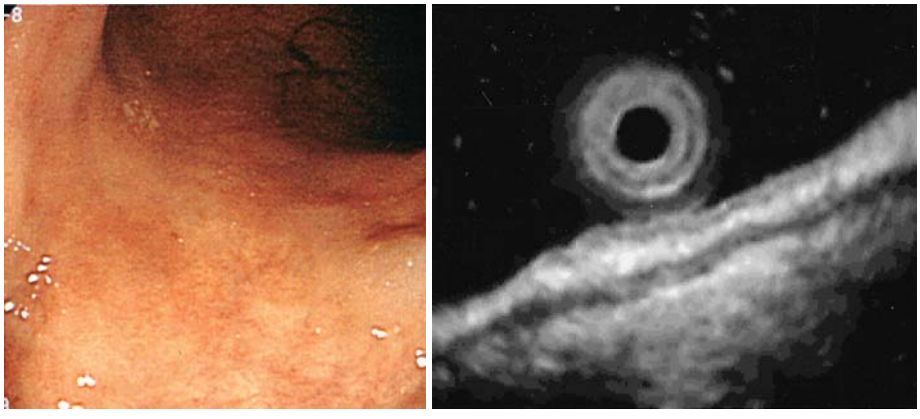

Fig. 2. a Case 1. After antibiotic therapy, no relapse of the tumor was shown on endoscopy. **b** After antibiotic therapy, on EUS, tumor regression was shown

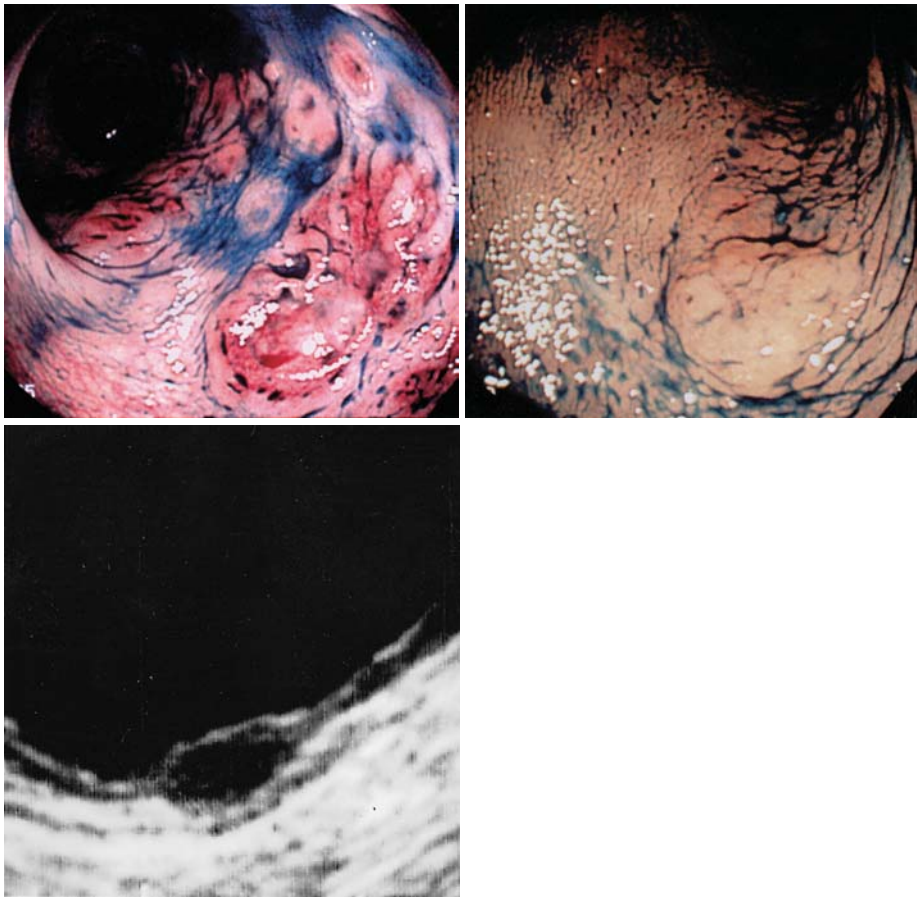

Fig. 3. a Endoscopic findings in case 2. Before antibiotic therapy, multiple flat tumors that were reddish in color were observed. **b** Endoscopic ultrasonography findings in case 2. The rectal tumor had infiltrated downward into the deepest part of the submucosa. **c** After antibiotic therapy, the rectal tumor had almost disappeared

antibodies. After obtaining informed consent from the patient, eradication therapy with amoxicillin 1500 mg and clarithromycin 800 mg per day was instituted for a period of 2 weeks. Three months after completion of the therapy, colonoscopy revealed continued regression of the tumor lesion. From the EUS findings at the same site, the presence of a residual lesion in the submucosal layer, as well as the muscular layer, was suspected, and the antibiotic regimen was repeated for 1 week. Five months later, apparent recurrence was endoscopically confirmed; therefore, the antibiotic therapy was once again given for 1 week. Throughout the 12-month follow-up period, no relapse was observed on endoscopy (Fig. 2a) or in the biopsies; on EUS, regression of the tumor was observed (Fig. 2b).

Case 2

In February 1997, an 80-year-old woman who was suffering from a serious form of heart disease underwent a colonoscopy because of anal bleeding. The procedure revealed diffuse reddish, erosive tumors, and a protruding mass lesion in the rectum (Fig. 3a). The patient was diagnosed with self-limited colitis and was given symptomatic treatment. However, no improvements were observed, and in August of the same year, for the purpose of further diagnosis, endoscopic mucosal resection (EMR) of the protruding mass lesion was performed. The EMR specimens showed the diffusely infiltrating growth of medium-sized atypical lymphocytes with round or irregular nuclei. Furthermore, the proliferation of centrocyte-like cells and lymphoepithelial lesions was observed. Immunostaining findings were CD20 (+), CD45RO (–), CD5 (–) and cyclin-D1 (–), and from these results the lesion was diagnosed as a low-grade MALT lymphoma. Total colonoscopic examination performed after hospitalization at our institution disclosed lesions in the terminal ileum and in the cecum, as well as in the sigmoid colon. On EUS, the rectal tumor had infiltrated downward into the deepest region of the submucosal layer (Fig. 3b). On chest X-ray films, abdominal CT scans, and gallium scintigraphy, neither swelling of the lymph nodes nor any infiltration into other organs was shown. Bone marrow findings also revealed no abnormalities; therefore, a diagnosis of stage IE was established. Upper gastrointestinal endoscopic examination showed no abnormal findings. The patient was confirmed as *H. pylori*-negative based on culture data, macroscopic examination of specimens, serum antibodies, and a rapid urease test (RUT). After obtaining informed consent from the patient, and in accordance with *H. pylori* eradication therapy, treatment consisting of amoxicillin 1500 mg and clarithromycin 800 mg per day was administered for a period of 2 weeks. Six months after completion of the eradication therapy, regression of the tumor lesions in both the terminal ileum and cecum was observed on colonoscopy, but minimal residual disease was present in the rectum (Fig. 3c). Follow-up was not conducted because of a worsening of the patient's heart disease condition.

Case 3

Case 3 has been reported elsewhere.[5] In July 1998, a 70-year-old woman presented herself to Tenyoukai Chuo Hospital complaining of abdominal discomfort. Following colonoscopic investigation, a hemispherical and protruding mass lesion, measuring 15 mm and covered with normal mucosa on the surface, was discovered in the rectum. Biopsies revealed no specific findings other than the infiltration of chronic inflammatory cells. The patient underwent follow-up colonoscopy in November of the same year, revealing enlargement of the lesion. On EUS, the lesion was found to have penetrated through the submucosal layer to the muscular layer. A biopsy investigation performed at the same time disclosed the diffusely infiltrative growth of medium-sized atypical lymphocytes with round or irregular nuclei. Immunostaining results were CD20 (+), CD45RO (–), CD10 (–), and bcl-2 (+), and these results were consistent with a diagnosis of low-grade MALT lymphoma. However, the results for CD5 and cyclin-D1, both of which are considered markers of mantle cell lymphoma, were positive and negative, respectively.

On chest X-ray films, abdominal CT scans, and gallium scintigraphy neither swelling of the lymph nodes nor any infiltration into other organs was shown; therefore, a diagnosis of stage IE was established. After obtaining informed consent from the patient, and in accordance with *H. pylori* eradication therapy, treatment consisting of amoxicillin 1500 mg and clarithromycin 800 mg per day was administered for a period of 2 weeks. Colonoscopy findings 10 days after completion of the antibiotic therapy showed regression of the tumor. Furthermore, a biopsy examination also revealed no abnormal findings. Throughout the 20-month follow-up, no recurrence was documented either by endoscopy or biopsy.

Discussion

Ever since Wotherspoon and colleagues[8] reported, in 1993, that *H. pylori* eradication by antibiotic administration caused regression of low-grade gastric MALT lymphomas, a series of similar reports have followed. Today, a consensus has largely been reached regarding the important link between gastric MALT lymphomas and *H. pylori*, and *H. pylori* eradication therapy has

become widely recognized as the treatment of first choice in the management of low-grade gastric MALT lymphoma. However, although *H. pylori* infection is present at a high frequency in patients with low-grade MALT lymphomas of the stomach, such lymphomas that are negative for *H. pylori* infection also exist.[9,10] Furthermore, some reports have described the usefulness of *H. pylori* eradication strategies in MALT lymphomas at gastrointestinal sites other than the stomach.[1–3,11,12] However, the mechanisms by which *H. pylori* eradication therapy exerts beneficial effects on tumor lesions distant from the stomach remain unknown.

The three patients reported in this study all tested negative for *H. pylori* infection by multiple examination methods, including the serum antibody technique. In these three patients, colonic MALT lymphoma regression was achieved within a short time after the administration of antibiotics. In most reports, MALT lymphomas of the gastrointestinal tract arise in the stomach, while those in the colon are rare. Thus, reported cases in which colonic MALT lymphoma regression was attained by *H. pylori* eradication therapy are very few and far between.[1–7] Table 1 provides a summary of all such reports. The ages of the patients in these reports (including our two patients) ranged from 33 to 80 years, with a mean age of 64.2 years. Except for one patient, all tumor lesions were found in the rectum. As for their morphological features, all tumors were of the protruding type. Tumor regression was not affected by the types of antibiotics administered or by the presence or absence of proton pump inhibitors. There were seven reported *H. pylori*-negative patients, in whom colonic MALT lymphoma regression was attained by the administration of antibiotics; these were the three cases reported by Nakase et al.[6] (including one case described by Inoue and Chiba[2]), the case reported by Oiya and coworkers,[7] and the three cases reported in this study. From these reports, the presence or absence of gastric *H. pylori* is considered to have had no apparent impact on the effectiveness of antibiotics against colonic MALT lymphomas. Based on the findings of Nakase et al.[6] and our present report, it is suggested that, by acting as antibody stimulators, certain microorganisms, other than *H. pylori*, that are sensitive to the multiple antibiotics administered, are deeply involved in the development of colonic MALT lymphoma in *H. pylori*-negative patients. However, as with other gastrointestinal organs, the colon is also exposed to massive antigen stimulation by its contents and their degradation products and other factors, in addition to various bacteria. Therefore, identification of the causative antigen for such stimulation is deemed difficult.

As a methodology for determining the therapeutic indication for *H. pylori* eradication therapy of gastric

Table 1. Reported cases of regression of colonic mucosa-associated lymphoid tissue lymphoma after antibiotic therapy

No.	Year	Author	Age (years)	Location of tumor	Configuration (size)	Invasion depth by EUS	Gastric *Helicobacter pylori* infection	Regimen
1	1997	Matsumoto[1]	72	Rectum	Protrusion	mp	Positive	P,A,C
2	1999	Inoue[2]	62	Rectum	Protrusion	m ~ sm	Negative	P,A,C
3	2000	Raderer[3]	67	Descending	Protrusion (1.5 cm)	—	Positive	P,C,M
4	2001	Inoue[4]	67	Rectum	Protrusion (1.1 cm)	sm	Positive	P,A,C
5	2002	Nakase[6]	66	Rectum	Protrusion	m ~ sm	Negative	P,A,M,T
6	2002	Nakase[6]	33	Rectum	Protrusion	—	Negative	A,C
7	2002	Hisabe (case 3)[5]	70	Rectum	Protrusion (1.5 cm)	mp	Negative	P,A,C
8	2003	Oiya[7]	54	Rectum	Protrusion (2.0 cm)	sm, slight	Negative	P,A,C
9	2004	Present case 1	71	Rectum	Protrusion (3.5 cm)	A_2	Negative	A,C
10	2004	Present case 2	80	Cecum, rectum	Protrusion (2.0 cm)	sm, massive	Negative	P,A,C

P, proton pump inhibitor; A, ampicillin; C, clarithromycin; M, metronidazole; T, tetracycline

MALT lymphomas, EUS methods have been reported.[13–15] According to these reports, *H. pylori* eradication therapy is ineffective against tumor lesions whose depth of penetration, as evaluated on EUS, reaches the deep region of the submucosal layer. On the other hand, tumors within the mucosa, or those that do not penetrate beyond the superficial region of the submucosal layer are described as good indications for *H. pylori* eradication therapy. However, in all the cases studied here, the tumors infiltrated not only into the deep region of the mucosal layer but also into the muscularis and adventitia, as documented by EUS. However, regression of the colonic MALT lymphomas was achieved after treatment with anti-*H. pylori* antibiotic therapy. This suggests the possibility that, in contrast to MALT lymphomas of the stomach, in which antibiotics are effective depending on tumor invasive depth the administration of antibiotics is beneficial for the management of MALT lymphomas of the colon, independent of tumor invasive depth.

Therefore, with colonic MALT lymphomas, appropriate antibiotic administration is considered the treatment of first choice. Due to the limited number of patients with this disease, however, further investigations of treatment approaches are required. In the future, therefore, more samples from such patients, focusing on the depth of penetration and clinical stages of the tumor lesions, need to be accumulated.

The success of the antibiotic treatment also suggests that MALT lymphomas may be caused by unknown luminal microorganisms other than *H. pylori.*

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