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CANCER BOARD CONFERENCE

Radical radiation therapy of primary rectal mucosa-associated lymphoid tissue lymphoma after bacteria elimination therapy

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Abstract Mucosa-associated lymphoid tissue (MALT) lymphoma is a subtype of non-Hodgkin's lymphoma and classified as marginal-zone B cell lymphoma. Although its most common organ is the stomach, it rarely arises in the rectum. Treatment for gastric MALT lymphoma has been established. However, primary rectal MALT lymphoma is so rare that standard therapy has not been established. We report the case of a 75-year-old man who was diagnosed rectal MALT lymphoma. Elevated lesions of the lower rectum were detected in a screening colonoscopy at a local clinic. The biopsy of the lesions revealed the lesions to be MALT lymphoma, and he was diagnosed with stage I E MALT lymphoma by Ann Arbor classification. Bacteria elimination was performed as initial treatment, but the lesion did not regress. Radiation therapy was chosen as second line therapy. A dose of 30 Gy to the small pelvic field in 15 fractions, followed by 10 Gy to the whole rectum in 5 fractions as boost was irradiated. Endoscopy at 20 Gy revealed a remarkable tumor reduction, and the lesions disappeared at the end of radiation therapy. Grade 1 urinary frequency and grade 1 diarrhea occurred during treatment, but the treatment was completed without cessation. The present case suggests that radiation therapy is one of the promising and safe options for rectal MALT lymphoma.

Keywords Rectal MALT lymphoma · Bacteria elimination therapy · Radiotherapy

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Case presentation

Dr. Oya (radiation oncologist, conference chairperson)

Good evening, everyone. Today, we would like to have a discussion on a primary rectal mucosa-associated lymphoid tissue (MALT) lymphoma case. MALT lymphoma was first conceptualized by Isaacson and Wright [1]. MALT lymphoma is a subtype of non-Hodgkin's lymphoma and classified as extranodal marginal-zone B cell lymphoma. Its most common origin is the stomach. MALT lymphomas arise from other diverse origins such as the salivary gland, thyroid, lung, and conjunctiva breast. However, primary rectal MALT lymphoma is very rare. Dr. Matsuyama, please begin the case presentation.

Dr. Matsuyama (radiation oncologist)

The patient is a 75-year-old man who has undergone screening colonoscopy at a local clinic once a year. He has no major past disease history except borderline diabetes mellitus followed-up without medication. Colonoscopic

examination revealed an elevated lesion 15 mm in diameter and 5 mm in height that appears to be a submucosal tumor at the Rb region of the lower rectum. The upper gastrointestinal endoscopy at this time did not reveal gastric lesions. He was diagnosed with rectal tumor and referred to the Department of Gastroenterology and Hepatology, Kumamoto University Hospital.

Dr. Kaku (gastroenterologist)

Barium enema examination showed an elevated lesion with smooth surface on the anterior wall of the lower rectum (Fig. 1). The lesion was soft and smooth on endoscopy, and another elevated lesion 6 mm in diameter was observed at approximately 2 cm caudal to the known lesion.

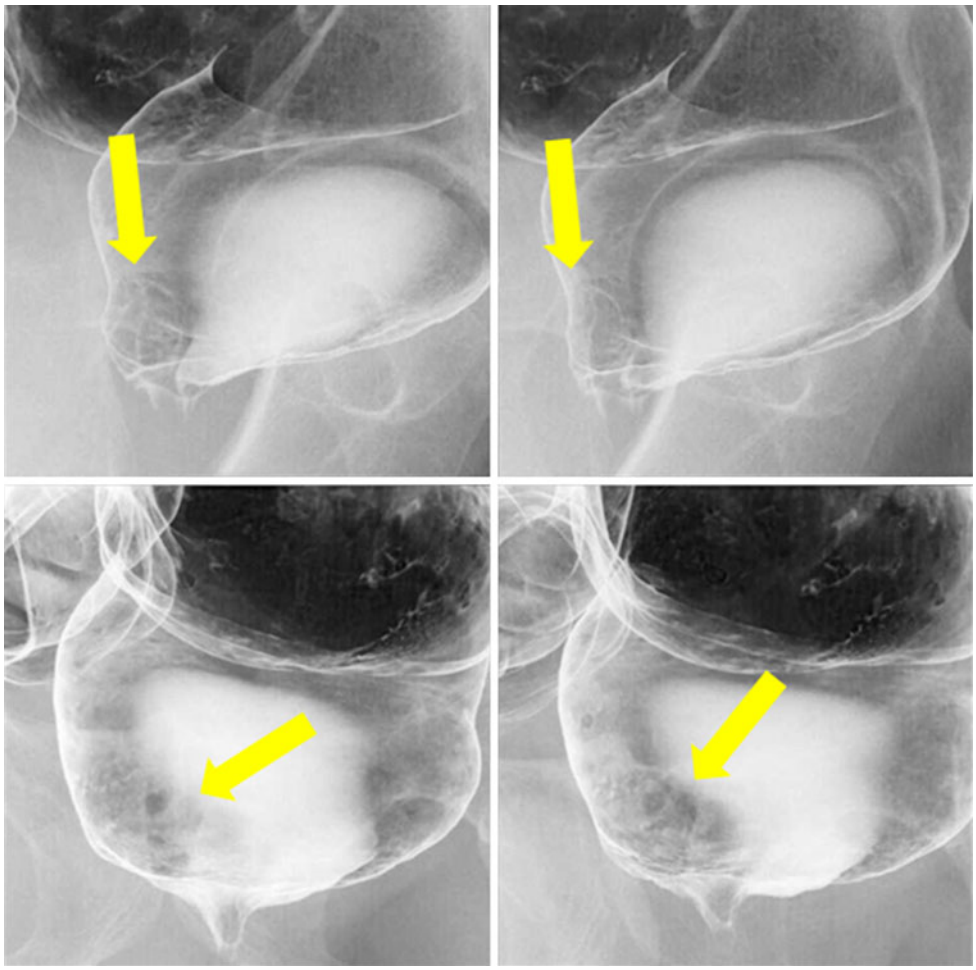

Fig. 1 Barium enema examination showed an elevated lesion (*arrows*) with smooth surface on the anterior wall of the lower rectum

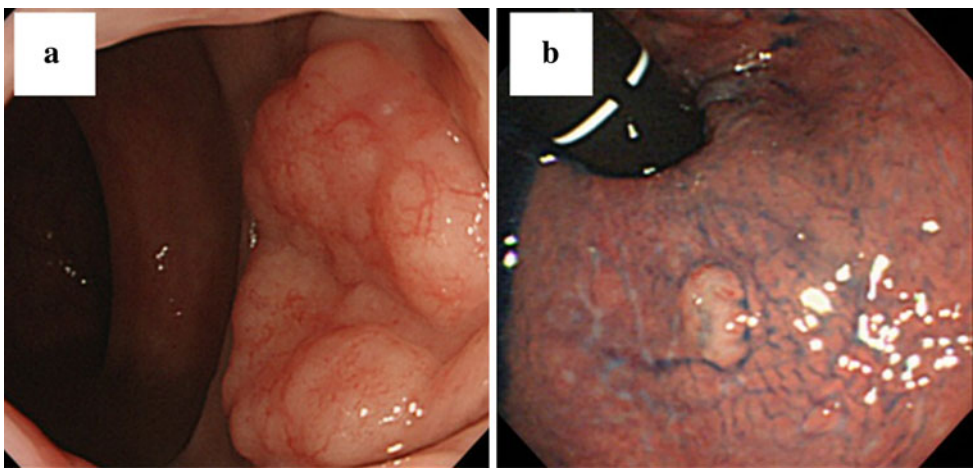

Fig. 2 Endoscopic examination showed elevated lesions 15 mm (**a**) and 6 mm (**b**) in diameter that appear to be submucosal tumors in the lower rectum

Vasodilation, tortuositas vasorum and caliber variation were observed (Fig. 2). In magnifying endoscopy, Kudo et al.'s [2] classification of pit pattern was Type I. Endoscopic ultrasound (EUS) revealed a hypoechoic lesion from the second to the third layer, and muscle layer was not involved (Fig. 3). From these findings, the lesions were diagnosed as tumors originating in the submucosa, such as leiomyoma, malignant lymphoma, or gastrointestinal stromal tumor (GIST). The lesions were biopsied.

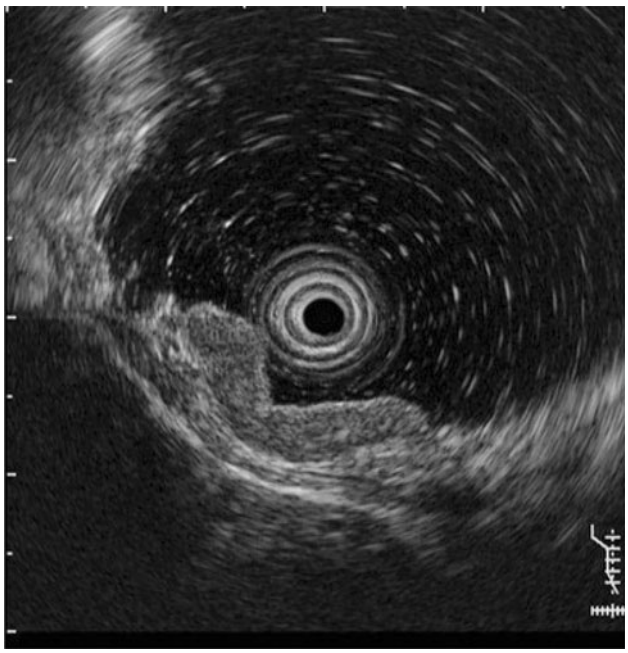

Fig. 3 Endoscopic ultrasound (EUS) revealed a hypoechoic lesion from the second to the third layer

Dr. Iyama (pathologist)

Histopathologic findings revealed diffuse infiltration of small to medium-sized lymphoid cells, having slightly irregular nuclei with moderately dispersed chromatin and inconspicuous nucleoli, and relatively abundant pale cytoplasm, resembling those of centrocytes. Lymphoepithelial lesion was partly observed. B cells were predominant on immunostaining, and lymphoma cells were positive for CD 20, CD 79 α, negative for CD3, CD45RO, CD5, CD10, cyclin D1. Histopathological diagnosis was MALT lymphoma of the rectum (Fig. 4).

Dr. Oya

The pathological diagnosis was MALT lymphoma. To decide treatment strategy, disease staging should be undertaken. Dr. Namimoto, please show the results of whole body evaluation.

Dr. Namimoto (radiologist)

Positron emission tomography (PET) with fluoro-deoxy-glucose (FDG) did not show the increased uptake to the rectal tumors. It is no wonder, considering the size and thickness of the lesions and the metabolically indolent nature of MALT lymphoma. Accumulation of FDG in MALT lymphoma is known to be generally weak [3]. No

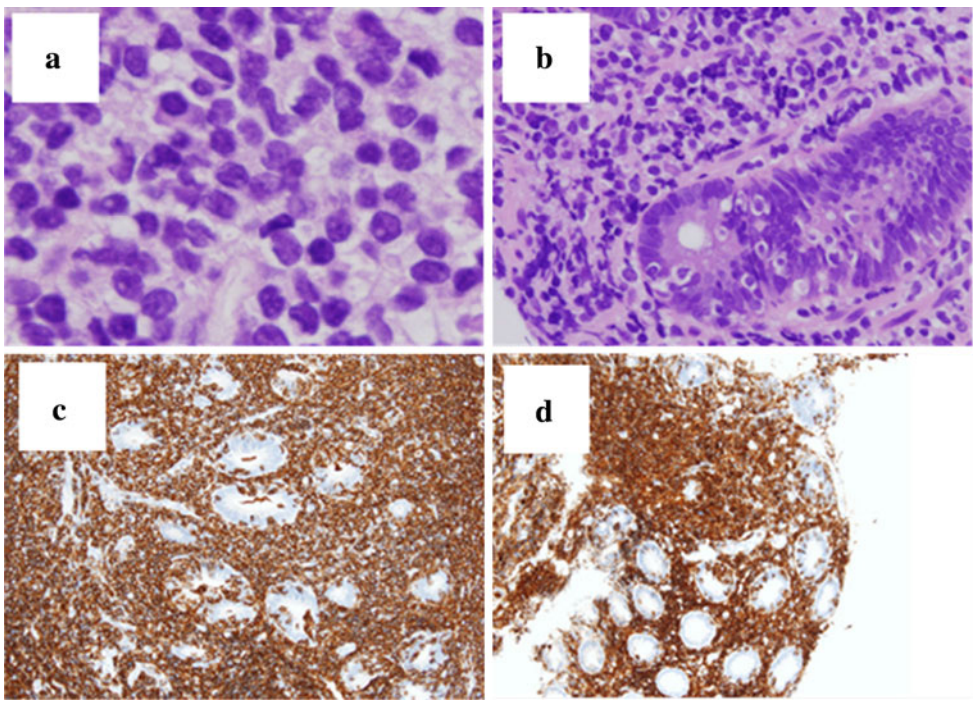

Fig. 4 Microscopic findings revealed diffuse infiltration of small to medium-sized lymphoid cells (**a**). Lymphoepithelial lesion was partly observed (**b**). B cells were predominant on immunostaining, and lymphoma cells were positive for CD20 (**c**) and CD79 α (**d**)

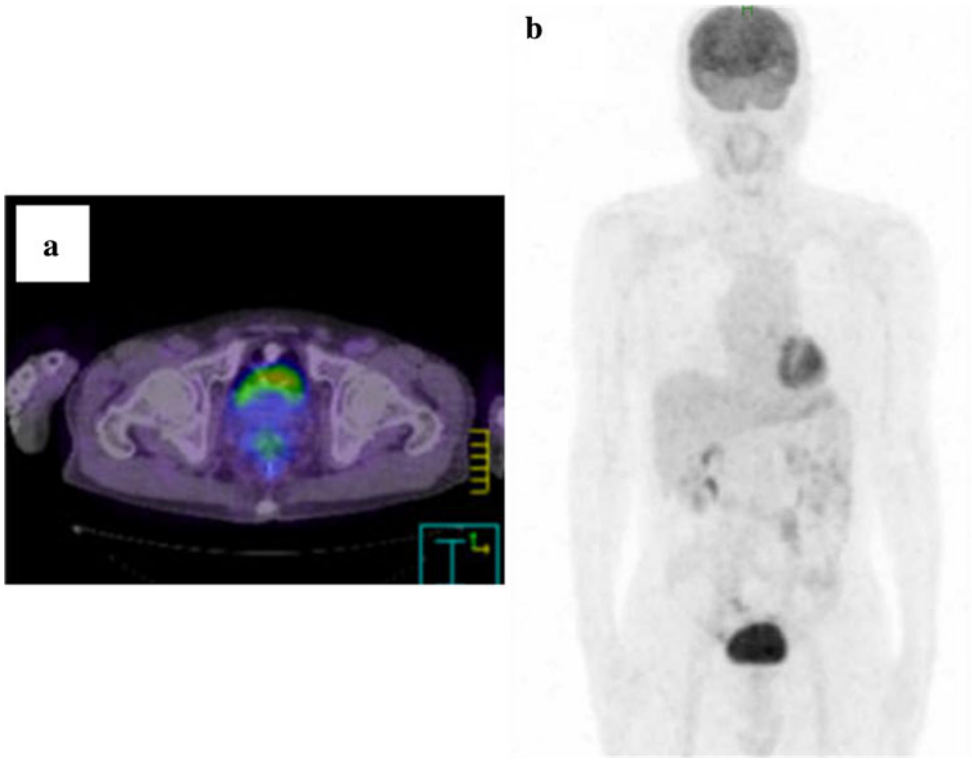

Fig. 5 Positron emission tomography (PET) with fluoro-D-glucose (FDG) did not visualize rectal tumors (**a**) nor any metastases (**b**)

abnormal accumulation was found in pelvic lymph node regions nor any other distant sites of the body (Fig. 5). In addition, whole body gallium-67 scintigraphy and whole body contrast-enhanced computed tomography (CT) were performed. They also depicted neither the known rectal tumors nor other involved sites. Imaging studies showed no evidence of systemic spread or multicentricity.

Dr. Kaku

No significant abnormality was observed in the physical examination of the patient. Laboratory data were mostly within the normal range except a slight elevation of hemoglobin A1c of 7.1 % (NGSP). Soluble interleukin-2 receptor level (357 U/mL) and lactate dehydrogenase (LDH) level (171 IU/L) were within the normal limit. From these results, the patient was diagnosed with stage I E rectal MALT lymphoma by Ann Arbor classification [4].

Dr. Oya

It is well established that approximately two-thirds of gastric MALT lymphoma is caused by chronic infection of *Helicobacter pylori*, and that bacteria elimination therapy is often effective for gastric MALT lymphoma [5]. Was the patient infected with *Helicobacter pylori*? How about the relationship between *Helicobacter pylori* infection and rectal MALT lymphoma?

Dr. Kaku

Urine antibody test for *Helicobacter pylori* of the patient was positive. Direct relationship between rectal MALT lymphoma and *Helicobacter pylori* remains unclear. However, there are several studies that described regression of rectal MALT lymphoma after *Helicobacter pylori* elimination therapy [6–9]. Treatment options for rectal MALT lymphoma include bacteria elimination therapy, radiation therapy, endoscopic mucosal resection (EMR), surgery, chemotherapy, rituximab monotherapy and active surveillance. Among them, bacteria elimination therapy was chosen as the initial treatment.

Dr. Oya

There are several options for rectal MALT lymphoma of the rectum. Why was bacteria elimination therapy chosen?

Dr. Kaku

Through discussion with hematologists and radiation oncologists, we concluded that four treatment options, bacteria elimination therapy, rituximab monotherapy, EMR, and radiation therapy, would be appropriately indicated for the present case, and bacteria elimination therapy is minimally intensive and inexpensive compared with other therapy.

Dr. Nosaka (hematologist)

Treatment strategy for rectal MALT lymphoma has not been established due to its rarity. It has basically low malignant potential and grows slowly. Considering such an indolent nature of the disease, the patient's age, the localized tumor status and the light tumor burden, a strategy of beginning with the least intensive therapy may be acceptable. Although there are some reports that describe regression of rectal MALT lymphoma after bacteria elimination therapy, they showed that it is not as effective for rectal MALT lymphoma as for gastric MALT lymphoma.

Dr. Kaku

This patient is a *Helicobacter pylori* positive case, suggesting potentially some efficacy of bacteria elimination therapy. Although the mechanism of effect of bacteria elimination therapy for non-gastric MALT lymphoma is not clear, controlling of systemic immune reaction by infection might achieve regression of tumor.

Dr. Nosaka

Was EMR also one of the candidates of the initial treatment?

Dr. Kaku

Yes, several previous reports demonstrated that localized rectal MALT lymphoma could be successfully treated by EMR [10]. We thought EMR was possible but difficult for this patient because of his multiple lesions, and we also had some apprehension of positive vertical margin due to primarily submucosal lesions.

Dr. Oya

How about radiation therapy and rituximab therapy?

Dr. Matsuyama

It is known that radiation therapy is very effective for limited stage MALT lymphoma originating from any organ [11, 12]. But, it is substantially a cytocidal therapy, and regarded to be more invasive than bacteria elimination therapy.

Dr. Nosaka

Rituximab monotherapy was reported to be effective for gastric MALT lymphoma [13] and also for rectal MALT lymphoma [14]. Its toxicity may be as low as bacteria elimination therapy. However, for this patient, it was not chosen as the initial treatment, considering that the lesions appeared to be limited to rectum.

Dr. Kaku

Thus, we offered the patient and his family bacteria elimination therapy as the initial treatment, because the pathological findings indicated low malignant potential, and it might be better to begin with the minimally invasive therapy, and EMR, radiation therapy, and rituximab therapy would be preserved as second-line therapeutic options. They consented to our presentation.

Dr. Oya

Please make a brief presentation of the clinical course.

Dr. Kaku

Bacteria elimination therapy was performed 4 days after the confirmation of the diagnosis with three drugs, lansoprazole 60 mg/day, amoxicillin 1500 mg/day and clarithromycin 400 mg/day for 7 days. After this therapy, the urea breath test became negative, suggesting the successful bacteria elimination. Endoscopic evaluation 1 week and 1 month after the completion of the therapy showed, however, no change in size of the lesions. At this time, the patient wished for immediate start of the next therapy. After a discussion with radiation oncologists, we decided to introduce radiotherapy as the second line treatment.

Dr. Oya

In spite of successful sterilization of *Helicobacter pylori*, there was no sign of tumor regression. In such a situation, how long can we wait for a delayed response?

Dr. Kaku

It is somewhat controversial. One of the previous reports showed that the average time from *Helicobacter pylori* eradication therapy to the regression of rectal MALT lymphoma was 3–4 months, while another report showed more rapid regression within 1 month after sterilization [14]. In the present case, it was difficult to wait longer, because the tumors did not show even the slightest sign of regression, and the patient strongly desired to receive another more intensive therapy. Therefore, we recommend radiation therapy.

Dr. Oya

Please explain about radiation therapy for MALT lymphoma.

Dr. Matsuyama

Radiation therapy has been reported to be very effective for limited stage gastric MALT lymphoma, either as the initial treatment or as the second line treatment for residual or persistent lesions after bacteria elimination therapy. On the other hand, radiation therapy for rectal MALT lymphoma has not been established. There are only a few case reports [15–17]. However, I thought radiation therapy could be safely and effectively performed for this patient, considering the tumor size, location, and the high radiation sensitivity of MALT lymphoma.

Dr. Nosaka

Radiation therapy and other possible treatment options including rituximab monotherapy were considered again. Adverse events of rituximab, such as fever, itching, headache, are usually mild, and severe toxicity is very rare. However, curability has not been established yet. Moreover, rituximab is expensive. As Dr. Kaku and Dr. Matsuyama said, radiation therapy might be the best as the second line therapy, also considering that the patient wished for rapid regression of the tumors.

Dr. Kaku

The patient chose radiation therapy, and then we asked Dr. Matsuyama for radiation therapy planning.

Dr. Oya

Dr. Matsuyama, how did you plan the radiation therapy in this case?

Dr. Matsuyama

A dose of 30 Gy to the small pelvic field in 15 fractions, followed by 10 Gy to the whole rectum in 5 fractions as boost was prescribed (Fig. 6). There is a general consensus that the total radiation dose of 30–36 Gy may be sufficient to control limited stage MALT lymphoma. In the present case, a slightly higher total dose of 40 Gy was prescribed, because the optimal radiation dose for rectal MALT lymphoma due to the rarity of the disease. In previous reports, prescribed dose ranged 30–45 Gy. Therefore, I selected a total dose of 40 Gy weighting curability. With regard to toxicity of radiation therapy, the adverse events of radiation therapy depend on radiation dose. In this case, we expected that 40 Gy in 20 fractions seldom causes severe late adverse events.

Dr. Oya

Is prophylactic nodal irradiation necessary?

Dr. Matsuyama

It is also controversial. In previous reports, irradiation fields varied from the rectum to the whole pelvic field [15–17]. Usually, prophylactic nodal irradiation is omitted in radiation therapy for gastric MALT lymphoma to reduce toxicity for surrounding radiosensitive organs, such as small intestine, kidneys and liver. In case of rectal lesions, the surrounding organs are considered to be generally less radiosensitive. Therefore, the planned radiotherapy, the first 30 Gy to small pelvis with a 4-portal field and 10 Gy boost to rectum would be unlikely to cause severe late toxicity.

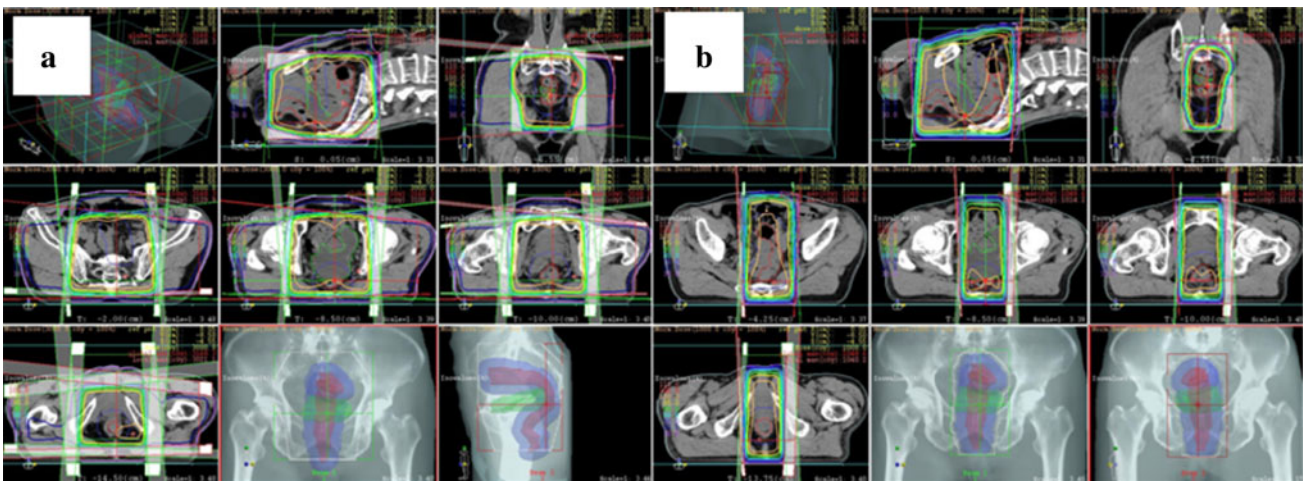

Fig. 6 Radiation therapy planning. **a** Initial plan: 40 Gy to small pelvic field. **b** Boost plan: 20 Gy to whole rectum

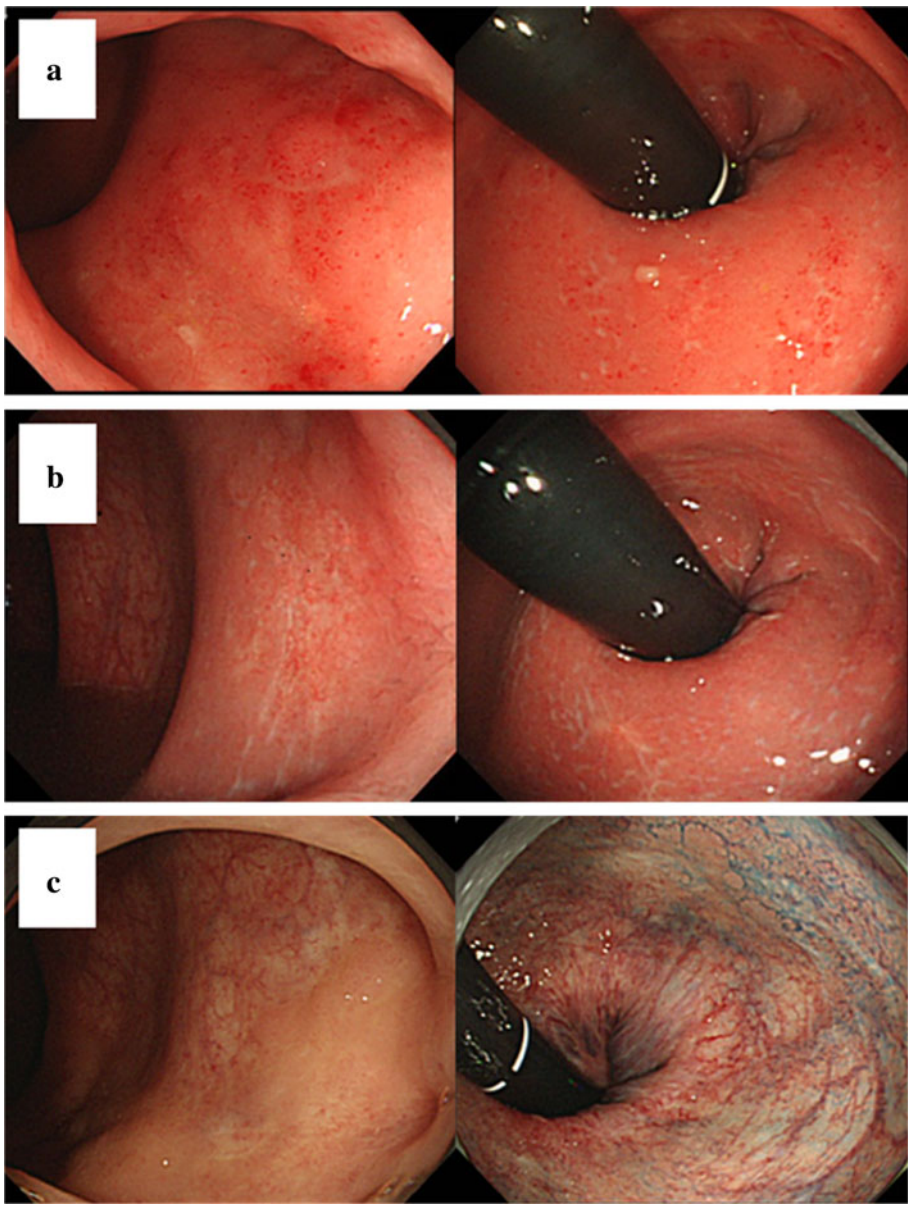

Fig. 7 Endoscopic examination at 20 Gy (**a**) and 40 Gy (**b**) showed remarkable efficacy. Follow-up endoscopic examination 30 months after radiation therapy showed scar without recurrence (**c**)

Dr. Oya

Was any adverse event observed during radiotherapy?

Dr. Matsuyama

Grade 1 urinary frequency and grade 1 diarrhea occurred during treatment, but the treatment was completed without cessation.

Dr. Oya

How about the response and the late adverse event?

Dr. Kaku

Endoscopy at 20 Gy revealed a remarkable tumor reduction, and the lesions disappeared at the end of radiation therapy. Endoscopy 30 months after radiation therapy showed complete response (Fig. 7). Follow up CT and FDG-PET did not detect any recurrence. No significant late toxicity has been observed.

Dr. Oya

Thank you very much. Please follow-up the patient further.

What we learned from this case conference

1. Although the most common site for MALT lymphomas of the gastrointestinal tract is the stomach, they rarely arise in the rectum.
2. Bacteria elimination therapy is minimally intensive and sometimes effective. In addition, radiation therapy, EMR and rituximab are attempted. However, treatment for rectal MALT lymphoma has not been standardized yet. We must know merits and demerits of each therapy and must be able to inform patients of those.
3. Although optimal radiation therapy for rectal MALT lymphoma has not been established, a dose of 40 Gy seems to be enough to achieve complete response.

Conflict of interest The authors declare that they have no conflict of interest.

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