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Signet Ring Cell Gastric Cancer Occurring after Radiation Therapy for *Helicobacter pylori*-Uninfected Mucosa-Associated Lymphoid Tissue Lymphoma

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Key Words
Helicobacter pylori · Signet ring cell carcinoma · Stomach neoplasms · B-cell lymphoma · Radiotherapy

Abstract
Helicobacter pylori infection is the major cause for mucosa-associated lymphoid tissue (MALT) lymphoma and gastric cancers. On the other hand, gastric cancers are known to arise from gastric mucosal atrophy. We here report a case of signet ring cell gastric cancer that developed after radiation therapy for MALT lymphoma in *H. pylori*-uninfected patient whose stomach did not show gastric mucosal atrophy. A 58-year-old female was referred to our hospital for treatment of gastric MALT lymphoma. This patient was not infected with *H. pylori*, and upper gastrointestinal endoscopy revealed that she did not have gastric mucosal atrophy but had submucosal tumor-like MALT lymphoma lesion in the anterior wall of the upper gastric body. Since conventional eradication therapy was ineffective, her whole stomach was irradiated as a second-line therapy. The MALT lymphoma lesion turned into complete remission state after the therapy. The patient was followed every 6 months by upper gastrointestinal endoscopy for 4 years as complete remission until a newly developed decolorized depressed lesion was detected in the greater curvature of the proximal antrum, a completely different location from the MALT lymphoma lesion. A biopsy specimen from the lesion contained signet ring cell carcinoma, and she was successfully treated by endoscopic submucosal dissection. No signs of recurrence have been detected so far. The radiation therapy for MALT lymphoma

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might be associated with the occurrence of this signet ring cell gastric cancer, and since MALT lymphoma is indolent in nature, this case suggests that careful consideration is required when choosing the second-line therapy for MALT lymphoma patients.

Introduction

Mucosa-associated lymphoid tissue (MALT) lymphoma is a B-cell non-Hodgkin lymphoma arising in lymphoid infiltrates at extranodal sites [1]. In the stomach, *Helicobacter pylori* infection is considered as one of the major causes of MALT lymphoma and gastric cancer [2]. *H. pylori* infection to the gastric mucosa causes chronic gastric inflammation leading to lymphocyte infiltration, which is considered to give rise to MALT lymphomas. Therefore, eradication of *H. pylori* with antibiotics is widely recognized as the initial treatment for *H. pylori*-infected MALT lymphomas [3].

Although over 90% of gastric MALT lymphomas were reported to be infected by *H. pylori*, there still are some *H. pylori*-negative MALT lymphomas [4]. *H. pylori* eradication therapy is also the first-choice treatment for *H. pylori*-negative MALT lymphomas, and radiotherapy or systemic chemotherapy is employed as the second-line therapy for cases that fail antibiotic therapy, although the long-term prognosis is still unclear [3].

Here we report a case of signet ring cell gastric cancer arising after radiation therapy for *H. pylori*-negative gastric MALT lymphoma.

Case Report

A 58-year-old female was referred to our hospital for the treatment of gastric MALT lymphoma in September 2006. Urea breath test, gastric biopsy specimens, rapid urease test and serum anti-*H. pylori* antibody indicated that this woman was not infected with *H. pylori*. Upper gastrointestinal endoscopy showed normal appearance, without mucosal atrophy or intestinal metaplasia, except for submucosal tumor-like lesion in the anterior wall of the upper gastric body (**fig. 1**a). Serum pepsinogen and biopsy specimens also indicated that this patient did not have gastric mucosal atrophy. The histopathological analysis of biopsy specimens taken from the lesion showed dense infiltration of atypical lymphocytes in the lamina propria of the gastric mucosa accompanied by formation of lymphoepithelial lesions (fig. 1b), leading to the diagnosis of MALT lymphoma. Bone marrow puncture revealed normocellular marrow with no lymphoma cell infiltration. Laboratory data, including serum soluble interleukin 2 receptor, gastrin and immunoglobulin levels, were within normal limits. Genetic analysis showed that this patient was negative for *API2/MALT1* translocation. The patient did not have systemic lymphoid lesions detected by computed tomography and gallium scintigraphy, thus we diagnosed this patient as stage I in the Lugano staging system [5].

Eradication therapy of *H. pylori* is broadly employed as the first choice for MALT lymphoma, even in *H. pylori*-uninfected patients [6]. Hence, the patient underwent standard 7-day course eradication therapy for *H. pylori* using Lansoprazole, amoxicillin and clarithromycin. Since the treatment was not effective for gastric MALT lymphoma lesion at 3 months after therapy, she was then treated with radiation therapy of the whole stomach as a second-line therapy (total 30 Gy) [7]. From 1 month after the completion of radiation therapy, the MALT lymphoma lesion lost its height and became a decolorized scar. Biopsies from the scar revealed that the MALT lymphoma was in complete remission (CR) state.

The patient was followed by endoscopy every 6 months for 4 years as CR until a newly developed decolorized depressed lesion in the greater curvature of the proximal antrum, a completely different

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location from the MALT lymphoma, was detected in August 2010 (fig. 2a, arrowhead). Although the MALT lymphoma was in CR, the biopsy specimen taken from this depressed lesion contained signet ring carcinoma cells (fig. 2b). Since the lesion was less than 20 mm in diameter and the depth of the lesion was considered to be not deeper than the mucosal layer by endoscopic ultrasonography, the patient was treated with endoscopic submucosal dissection (Sig, depth m, ly0, v0, VM–, LM–) and the lesion was completely removed. Absence of *H. pylori* in the stomach was reconfirmed by urea breath test, serum anti-*H. pylori* antibody, biopsy specimen and rapid urease test. The patient is still followed up every 6 months. MALT lymphoma is still in CR, and so far no other gastric lesions have been detected.

Discussion

There have been prior reports regarding the coexistence of MALT lymphoma and gastric cancers, but all cases were infected with *H. pylori* [8–10]. Among these reports, Copie-Bergman et al. proposed that gastric cancers arise from MALT lymphoma lesions in response to the residual lymphoma cells [10]. This was not the case in our patient since her gastric cancer arose from the mucosa where MALT lymphoma lesions were not observed. In addition, this patient was not infected with *H. pylori* and did not have gastric mucosal atrophy, hence it is very unlikely that *H. pylori* was spontaneously eradicated by severe gastric mucosal atrophy. Since gastric cancers seldom arise from the stomach of *H. pylori*-uninfected patients in Japan [11], it is possible that the radiation therapy had some responsibility for the occurrence of signet ring cell gastric cancer. There have been some prior reports regarding the correlation between radiation and signet ring cell cancer. Tamai et al. reported that rectal cancer developed in 4 patients who underwent pelvic radiation therapy against cervical cancer, and one of the developed cancer was signet ring cell carcinoma [12]. In addition, Watanabe et al. showed that radiation can induce signet ring cell gastric cancers in irradiated hypocatalasemic mice [13]. In their study, they showed that signet ring cell gastric cancers arose in 5 out of 22 irradiated mice while none of the unirradiated mice developed gastric cancer. These prior reports suggest the possibility of radiation therapy as one of the causes for signet ring cell gastric cancers.

To the best of our knowledge, we were unable to find any report regarding the coexistence of MALT lymphoma and signet ring cell gastric cancer in *H. pylori*-uninfected patients. Hence, our speculation for radiation therapy as the cause of signet ring cell gastric cancer might not be far-out. Since the long-term outcomes of radiation therapy for gastric MALT lymphomas are still unknown, careful follow-up is indispensable.

In conclusion, we here report a thought-provoking case of signet ring cell gastric cancer occurring in a radiation-treated MALT lymphoma patient. Since MALT lymphoma is indolent in nature [14], this case suggests that careful consideration is required when choosing the therapy for a MALT lymphoma patient who is resistant to *H. pylori* eradication therapy.

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Disclosure Statement

The authors have no conflicts of interest.

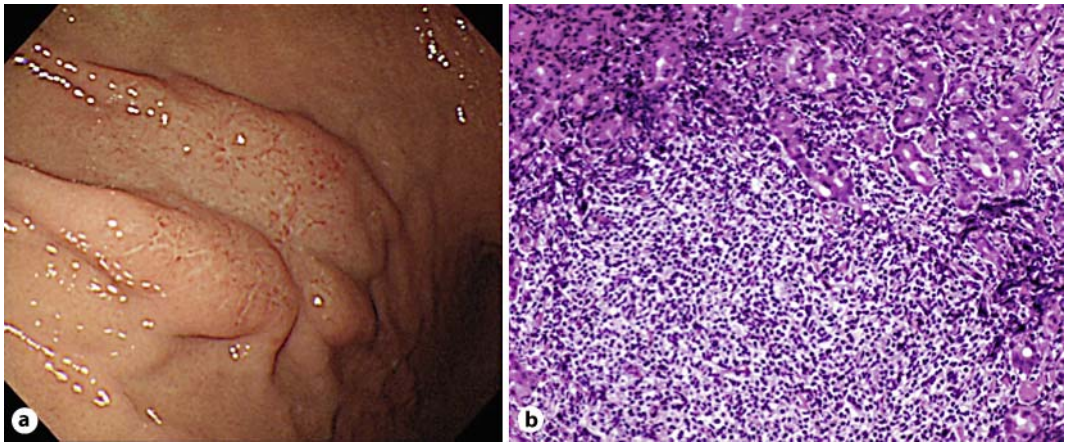

Fig. 1. Endoscopic and histological finding of pretreated MALT lymphoma lesions. **a** Submucosal tumor-like MALT lymphoma lesion in the anterior wall of the upper gastric body. **b** Lymphoepithelial lesions are observed in the biopsy specimen.

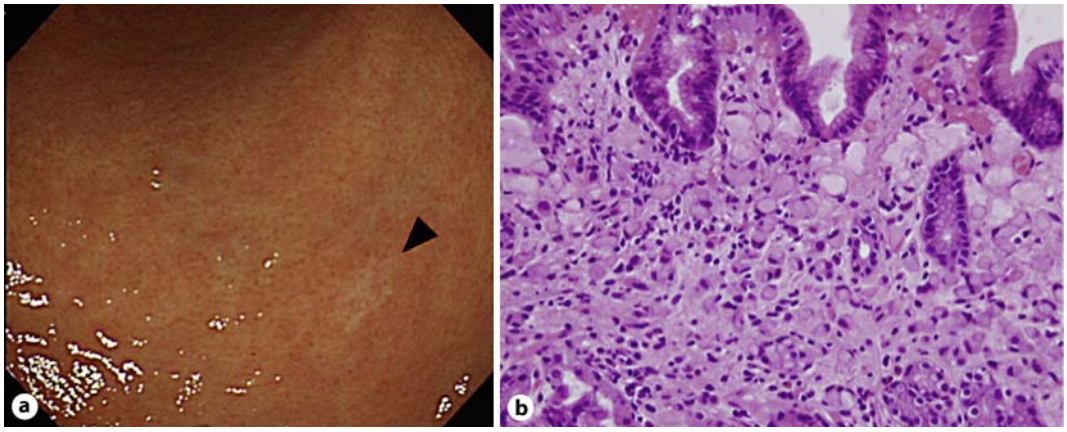

Fig. 2. Endoscopic and histological finding of the signet ring cell gastric cancer lesion. **a** Decolorized depressed lesion in the greater curvature of the proximal antrum. **b** Signet ring carcinoma cells were observed in the biopsy specimen.

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