The Progression of Esophageal Mucosa-associated Lymphoid Tissue Lymphoma after Helicobacter pylori Eradication Therapy: A Case Report and Discussion of Therapeutic Options

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Abstract:
A 50-year-old woman with epigastric discomfort was referred to our hospital. Esophagogastroduodenoscopy showed flat, elevated, submucosal tumor-like lesions in the esophagus. Extranodal marginal zone lymphoma of the mucosa-associated lymphoid tissue (MALT lymphoma) of the esophagus was diagnosed based on the examination of an endoscopic biopsy specimen. Computed tomography showed the enlargement of a lymph node in the gastric cardia. The present case showed disease progression despite Helicobacter pylori eradication therapy and achieved partial remission after rituximab monotherapy. The patient remained in partial remission for 20 months. This case suggests that esophageal MALT lymphoma with lymph node involvement does not respond to H. pylori eradication therapy and that it requires systemic treatment.

Key words: eradication therapy, esophagus, Helicobacter pylori, MALT, rituximab

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Introduction

The gastrointestinal tract is the most commonly involved extranodal site in patients with non-Hodgkin lymphoma (1, 2). Within the gastrointestinal tract, malignant lymphoma most frequently occurs in the stomach; esophageal occurrence is observed in <1% of patients with gastrointestinal lymphoma (2). Gastric mucosa-associated lymphoid tissue (MALT) lymphoma is well known to be associated with Helicobacter pylori (Hp) infection, and Hp eradication is accepted as a first-line therapy for localized gastric MALT lymphoma (3). A few cases of patients with esophageal MALT lymphomas who achieved remission after Hp eradication therapy have been reported (4, 5). However, the efficacy of Hp eradication therapy has not been elucidated for patients with esophageal MALT lymphoma because there are few reports of patients who have undergone this treatment.

In this report, we describe the case of a patient with primary esophageal MALT lymphoma who had tumor enlargement after Hp eradication therapy and subsequently achieved partial remission (PR) with four cycles of rituximab.

Case Report

A 50-year-old woman with epigastric discomfort was referred to our hospital. Her pertinent medical history only included vasospastic angina, and she had no history of any autoimmune disease, alcohol abuse, or smoking.

Esophagogastroduodenoscopy (EGD) revealed flat, elevated, submucosal tumor-like lesions covered with a faded, smooth, normal mucosa in the upper, middle, and lower thoracic esophagus (Fig. 1A-C). The lesions discontinuously and craniocaudally extended anterior to the right wall and had an indistinct vascular pattern. Magnifying narrow-band imaging endoscopy revealed that the intrapapillary capillary loop on the surface of the lesions was normal; however, ab-
normal blood vessels accompanied by vasodilation or tortuositas vasorum were recognized (Fig. 1D). Endoscopic ultrasonography showed a heterogeneous hypoechoic mass located in the submucosal layer (Fig. 1E). $^{18}$F-Fluorodeoxyglucose (FDG) positron emission tomography-computed tomography demonstrated an increased FDG uptake in the middle and lower esophagus and enlargement of a lymph node in the gastric cardia (15×10 mm) without FDG accumulation (Fig. 2). A histological examination of endoscopic biopsy specimens showed the aggregation of small or medium lymphoid cells. Immunohistochemistry revealed that they had a low Ki-67 index, were positive for CD20, and negative for CD5, CD10, and cyclin D1 (Fig. 3). Based on these findings, we diagnosed the patient with extranodal marginal zone lymphoma of the MALT of the esophagus with local nodal involvement.

The patient had closed-type atrophic gastritis and Hp infection was detected on a hematoxylin and eosin-stained specimen of the gastric mucosa. Furthermore, a rapid urease test was positive. Thus, the patient initially received Hp
eradication therapy with vonoprazan (40 mg), amoxicillin (1,500 mg), and clarithromycin (800 mg) daily for 1 week. A $^{13}$C-urea breath test was negative at 5 weeks after eradication. However, EGD performed at 12 weeks after $H. pylori$ eradication showed the enlargement of the esophageal lesions (Fig. 4). On computed tomography images, the esophageal lesion was demonstrated as a well-circumscribed enhancing mass (Fig. 4B), and the lymph node in the gastric cardia remained stable (Fig. 4C). The patient was subsequently treated with four cycles of rituximab (375 mg/m$^2$) and achieved a PR with a reduction in the size of the esophageal lesions and lymph node (Fig. 5). A PR has been maintained for 20 months.

**Discussion**

Primary esophageal lymphoma is a rare tumor, and there only 25 case studies of MALT lymphoma in the esophagus have been reported to date (4, 5, 6-28). In the previously reported cases, esophageal MALT lymphoma was treated with surgical resection (7-12), rituximab and/or chemotherapy (12-19, 27, 28), radiotherapy (8, 12, 20-22, 28), endoscopic resection (20-26), and $H. pylori$ eradication therapy (4, 5, 7, 8, 12, 13, 27); however, a standard treatment remains to be established.

The pathogenesis of MALT lymphoma is associated with chronic infection and inflammation (29). $H. pylori$ infection is
found in 50-100% of patients with gastric MALT lymphoma (30), and 60-90% of patients with gastric MALT lymphoma achieve complete remission (CR) after *Hp* eradication (31). In the clinical practice guidelines, *Hp* eradication therapy is described as a first choice for treating localized gastric MALT lymphoma (32, 33). However, the association between esophageal MALT lymphoma and *Hp* infection remains controversial. Four cases in which *Hp* eradication therapy was administered for esophageal MALT lymphoma have been reported (Table); two patients with localized disease achieved a CR after *Hp* eradication therapy (4, 5), whereas another case with lymph node involvement was treated with *Hp* eradication followed by rituximab (13). The other case had MALT lymphoma in the esophagus and stomach and required chemotherapy after *Hp* eradication (27). In the present case, tumor progression was observed during a relatively short period (12 weeks) after *Hp* eradication. These results indicate that *Hp* eradication may be effective for treating esophageal MALT lymphoma confined to the gastrointestinal tract, whereas esophageal MALT lymphoma involving the lymph nodes or other organs requires systemic chemotherapy and/or rituximab. Consequently, we recommend close follow-up [e.g., EGD with multiple biopsies 2-3 months after *Hp* eradication (3)], for patients with esophageal MALT lymphoma and additional treatments should be considered for patients with progressive disease.

Although tumor regression is sometimes recognized after *Hp* eradication therapy for non-gastric MALT lymphoma (4, 5, 34-37), the mechanism has remained to be elucidated. The regression of colorectal MALT lymphoma after the administration of drugs used for *Hp* eradication has been reported, even in patients who were negative for *Hp* infection (35, 37), suggesting that unknown, antibiotic-sensitive microorganisms (other than *Hp*) are involved in the development of non-gastric MALT lymphoma. However, further investigation is required to reveal the mechanisms underlying the effects of *Hp* eradication therapy and its efficacy in pa-
tients with non-gastric MALT lymphoma. In addition, there is no evidence to support eradication therapy in cases with extranodal involvement; thus, the immediate start of oncological treatment should be considered if no signs of regression are seen in such patients.

With regard to the treatment options for non-gastric MALT lymphoma (all stages), chemotherapy, immunotherapy, or a combination of both was suggested by the European Society for Medical Oncology (ESMO) consensus conferences (33). Radiotherapy was only considered to be a reasonable option for localized lymphomas (33). However, no definitive evidence has been found in favor of any of these modalities in the treatment of localized non-gastric MALT lymphoma. In addition, there is no standard chemotherapy regimen. There are seven reported cases of rituximab and/or definitive evidence has been found in favor of any of these reasonable option for localized lymphomas (33). Radiotherapy was only considered to be a reasonable option for localized lymphomas (33). However, no definitive evidence has been found in favor of any of these modalities in the treatment of localized non-gastric MALT lymphoma. In one case, a PR was achieved in a patient treated with cyclophosphamide, vincristine, and prednisone (CVP) therapy (14), while a PR was achieved in a patient treated with cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) therapy (18). Two of the four patients treated with rituximab combined CHOP (R-CHOP) therapy achieved a CR (15-17, 19). From these results, chemotherapy with and without rituximab might be more effective for achieving a CR. However, rituximab monotherapy might be a feasible option for disease control in patients with non-progressive MALT lymphoma because it is not necessary to achieve a CR in such cases (23).

Esophageal MALT lymphoma is a rare tumor and may be difficult to diagnose at an early stage. Oguzkurt et al. reported that the radiological findings of esophageal lymphoma may vary, but that the following characteristics may lead radiologists to suspect lymphomatous involvement: (i) thickened mucosal folds, (ii) submucosal nodules accompanying a tumor mass, (iii) multiple craters and erosions, and (iv) a tumor mass without narrowing or stricture formation (38). In a recent report that reviewed 14 patients with esophageal MALT lymphoma, the endoscopic findings of 11 patients showed submucosal tumor-like lesions; nine of these had cranio-caudal extension (22). The present case showed both of these endoscopic findings, and we additionally observed the presence of abnormal blood vessels similar to a tree-like appearance, which is a typical characteristic of gastric lesions in MALT lymphoma (39, 40). This characteristic was recently reported in an esophageal lesion by Kudo et al. (25). These radiological and endoscopic characteristics may be helpful in detecting esophageal MALT lymphoma lesions, and should prompt endoscopists to perform a biopsy to obtain specimens for histological examination.

Taken together, the patient in the present case showed disease progression of esophageal MALT lymphoma after Hp eradication therapy and achieved a PR after the initiation of rituximab monotherapy, indicating that close follow-up is preferable, even after Hp eradication therapy, because responses may vary among patients.

The authors state that they have no Conflict of Interest (COI).

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