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A primary esophageal MALT lymphoma patient with *Helicobacter pylori* infection achieved complete remission after *H. pylori* eradication without anti-lymphoma treatment

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ABSTRACT

Primary esophageal lymphoma is an extremely rare disease. We report a 76-year-old woman with esophageal lymphoma who achieved remission after *Helicobacter pylori* (HP) eradication. Esophagogastroduodenoscopy (EGD) revealed a mass in the lower esophagus, and she was diagnosed with stage IE mucosa-associated lymphoid tissue (MALT) lymphoma. She rejected any anti-lymphoma treatment except for HP eradication. Follow-up EGD demonstrated the disappearance of the esophageal MALT lymphoma 2 months after HP eradication, and she remained in remission for more than 3 years. Our results demonstrate that HP eradication may be effective as initial therapy in primary esophageal MALT lymphoma patients with HP infection.

1. Introduction

Esophageal lymphoma occurs mostly secondary to cervical and mediastinal lymph node invasion or contiguous invasion from gastric lymphoma [1], and thus primary esophageal lymphoma (PEL) is extremely rare, comprising less than 1% of primary gastrointestinal lymphomas [2]. The etiology of PEL is unknown, although HIV infection is thought to be one probable risk factor because several papers reported that some PEL patients were infected with HIV. The pathological subtypes of PEL are MALT lymphoma or diffuse large B cell lymphoma in most cases and other B, T, or NK cell lymphoma and Hodgkin lymphoma in a few cases. PEL patients complain of non-specific symptoms, i.e., epigastric pain, dysphagia, and B symptoms.

MALT lymphoma appears in association with chronic inflammation induced by persistent infection and autoimmune diseases such as *Helicobacter pylori* (HP) infection and Hashimoto's thyroiditis, respectively. Gastric MALT lymphomas are well known to be associated with HP infection, although there are very few cases of localized esophageal MALT lymphoma in HP-infected patients. Here, we present a patient with primary esophageal MALT lymphoma who achieved complete remission without anti-lymphoma treatment after HP eradication therapy and has remained in remission for more than 3 years. The literature on PEL is also reviewed to show the relationship between PEL and HP infection.

2. Case presentation

A 76-year-old woman visited our hospital with complaints of chest tightness after eating and epigastric discomfort for more than 10 days. Findings of physical examinations were completely normal, with no palpable swelling of the lymph nodes, liver, and spleen. Laboratory tests revealed slight leukocytosis and anemia, with normal levels of both serum lactate dehydrogenase and soluble interleukin-2 receptor. The level of anti-HP immunoglobulin G antibody was elevated. Her medical history included atrophic gastritis diagnosed by esophagogastroduodenoscopy (EGD) 5 years previously, although she had not received HP eradication therapy.

EGD revealed a fur-coated 2 cm mass negatively stained with iodine in the lower esophagus, 34 cm from the incisors (Fig. 1A), and no lymphoma involvement of the stomach or Barrett's change at the esophageal-gastric junction. Standard endoscopic biopsies were performed, and the histological findings showed mid-sized lymphocyte invasion mainly under the squamous epithelium and partially in the squamous epithelium. There was no follicular dendritic cell meshwork and lymphocyte aggregation, showing that it was not a reactive germinal center. The dyskaryosis was not severe, and lymphocytes formed a lymphoepithelial lesion. No HP organisms were identified. These lymphocytes were immunohistochemically positive for CD20 and CD79a, and negative for CD5, CD10, and BCL2 (Fig. 2). Histological

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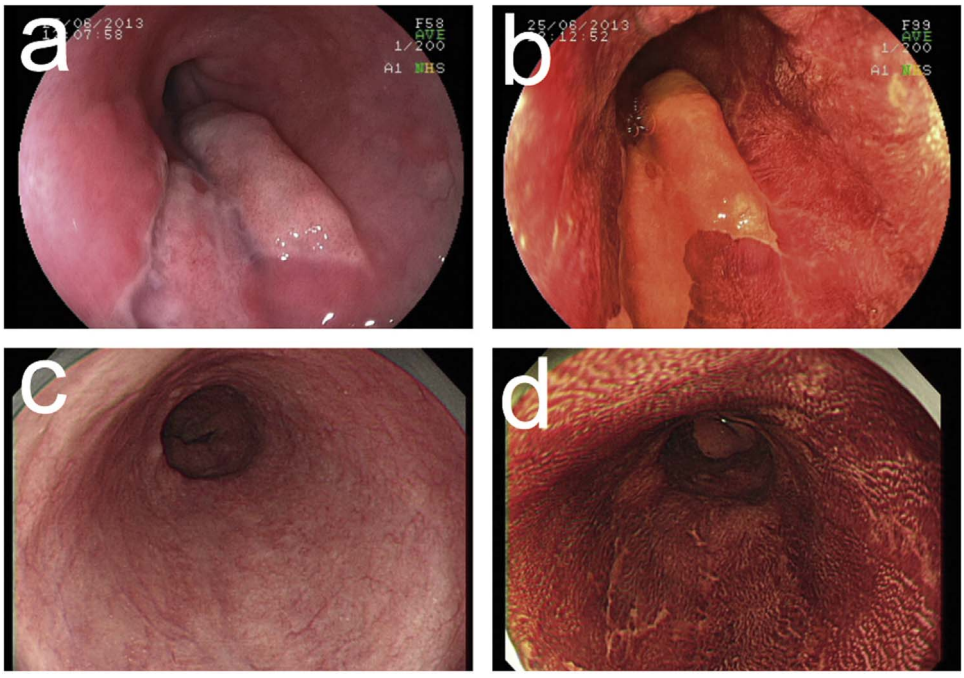

Fig. 1. Endoscopic findings of the esophagus. EGD showed a mass in the lower esophagus (a) and it was negative in iodine staining (b). The mass disappeared after HP eradication therapy (c) and there was no negative area of iodine staining (d).

findings of infiltrating atypical lymphoid cells were consistent with MALT lymphoma. Fluorescence in situ hybridization analysis of formalin-fixed paraffin-embedded tissue sections showed no split signal for MALT1. 18F-fluorodeoxyglucose (FDG) positron-emission tomography/computed tomography (PET-CT) demonstrated increased FDG uptake in the middle and lower esophagus, corresponding with the MALT lymphoma detected, and there were no other positive findings (Fig. 3). On the basis of these findings, the patient was diagnosed with MALT lymphoma of the esophagus, stage IA.

The patient refused either radiation therapy or systemic chemotherapy including rituximab and thus was initially treated with antibacterial therapy for HP infection. The first-line therapy consisted of lansoprazole 30 mg, amoxicillin 750 mg, and clarithromycin 200 mg twice daily for 1 week. After 2 months of treatment, the ^{13}C-urea breath test remained positive, although follow-up EGD and CT scanning showed complete disappearance of the mass (Fig. 1B). A second course of HP eradication therapy was administered, consisting of lansoprazole 30 mg, amoxicillin 750 mg, and metronidazole 250 mg twice daily for 1 week. The proton pump inhibitor was discontinued after the second course of therapy. The second ^{13}C-urea breath test performed 9 weeks

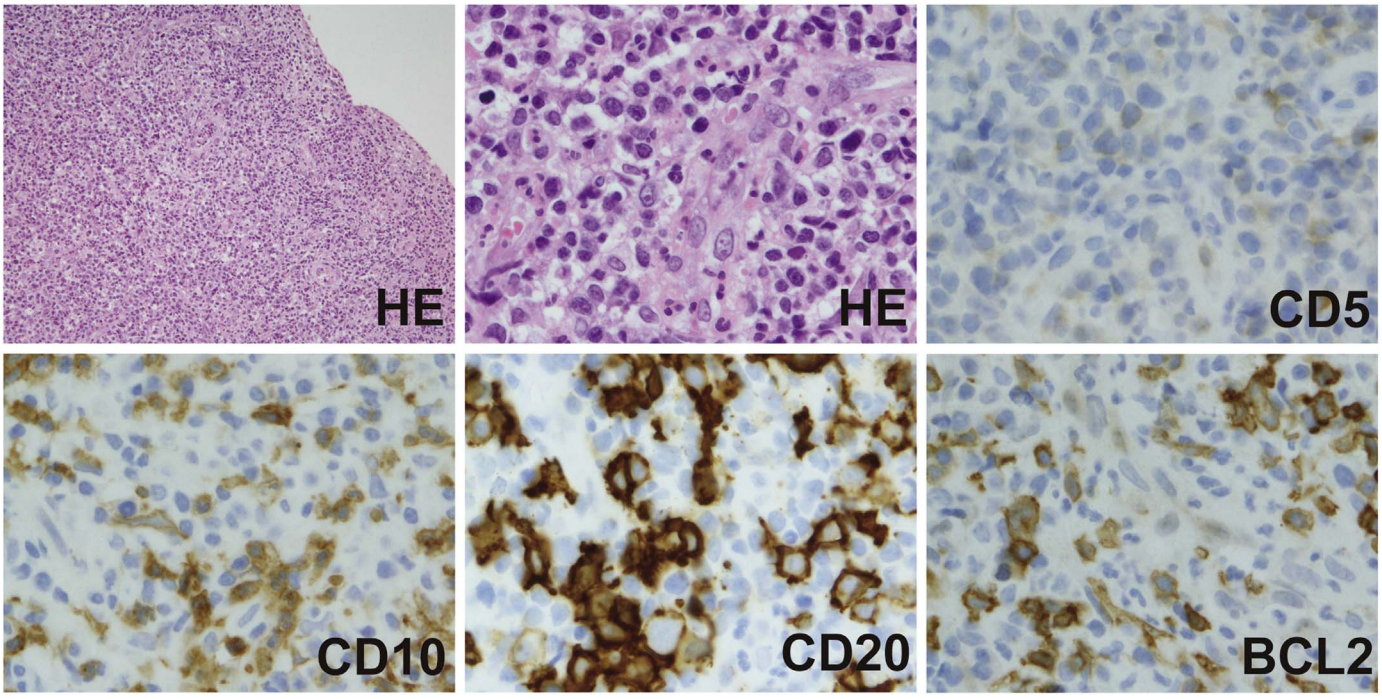

Fig. 2. Histological findings of the esophageal tumor. The atypical cells were positive for CD20 and CD79a and negative for CD5, CD10, and BCL2.

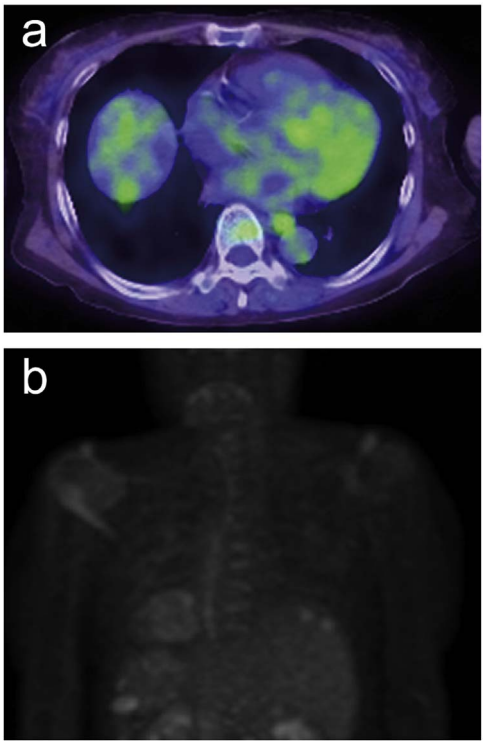

Fig. 3. FDG positron-emission tomography at diagnosis. (a) The coronal slice of PET-CT showed FDG uptake in the esophagus. (b) 3D image of FDG PET showed FDG uptake in the middle to lower esophagus.

after the second course of eradication therapy was negative. She has remained in complete remission for more than 3 years.

3. Discussion

We treated a primary esophageal MALT lymphoma patient who achieved complete remission after HP eradication therapy without any anti-lymphoma treatment such as chemotherapy and radiation. In this case, although no HP infection of the esophagus was detected, the lymphoma disappeared after the first insufficient eradication. She remained in complete remission for more than 3 years after the successful second eradication.

In a PubMed literature search, 37 PEL cases in stage I, without HIV infection, were reported in English and Japanese. The median age was 59 (range, 17–83) years with male dominancy (male: female=25:13). Although PEL had various tissue types, only 12 (32.4%) primary esophageal MALT lymphomas in stage I were reported (Table 1). Only one primary esophageal MALT lymphoma case with HP infection from other institution was reported in addition to ours.

Localized gastric MALT lymphoma with HP infection without t(11;18) translocation was reported to regress completely after HP eradiation therapy [3], and HP-negative gastric MALT lymphoma patients were treated with local radiation therapy or endoscopic mucosal resection, while a few received systemic chemotherapy. On the other hand, no standard treatment has been established for patients with localized primary esophageal MALT lymphoma. Six of 12 reported cases were treated with endoscopic resection, and 2 patients received rituximab therapy consisting of rituximab alone for one and rituximab in combination with radiation for the other (Table 1). Three patients with HP infection were treated with HP eradication therapy and either rituximab or resection or resection +radiation. Because no patient was treated with HP eradication alone among the previous reports, the role of HP eradication is unclear in esophageal MALT lymphoma. All PEL cases were reported to survive, although the observation periods were short.

Table 1
Clinical characterisitics of previously reported primary esophageal MALT lymphomas.

Patient no.	Age	Gender	Site	Gross appearance	Therapy	Clinical course	HP infection	Reference
1	70	F	Middle	Submucosal tumor	Resec	3 years, alive	Negative	Yano S et. al. Ann Hematol. 2009;88:703
2	63	F	Middle to lower	Submucosal tumor	ND	ND	ND	Nishiyama Y et. al. Ann Nuel Med. 1999;13:419
3	50	M	Middle	Mass	Resec	12 months, alive	Negative	Bardisi ES et. al. Ann Med Surg (Lond). 2014;3:39
4	66	M	Lower	Submucosal tumor	Resec	alive	Negative	Kudo K et. al. Dig Endosc. 2014;26:478
5	59	F	Upper	Submucosal tumor	Resec	2 years, alive	Negative	Baek DH et. al. Gastrointest Endosc. 2012;75:1282
6	83	F	Upper	Submucosal tumor	Resec	22 months, alive	Negative	Hosaka S et. al. Gut. 2002;51:281
7	74	M	Middle	Submucosal tumor	RT	alive	Negative	Kitamoto Y et. al. J Clin Gastroenterol. 2003;36:414
8	37	M	Middle	Chronic ulcer	RT+rituximab	6 months, alive	ND	Malik AO et. al. World J Gastrointest Endosc. 2013;5:446
9	70	M	Upper	Submucosal tumor	HP eradication+rituximab	6 months, alive	Positive	Tsujii Y et. al. Dis Esophagus 2013;26:349
10	56	F	Lower	Submucosal tumor	Resec+HP eradication	alive	Positive	Ling T et. al. Gastroenterology 2014;147: e8
11	49	M	Lower	Submucosal tumor	Resec	alive	Negative	Miyazaki T et. al. Hepatogastroenterology 2004;51:750
12	53	M	Lower	Submucosal tumor	Resec+RT+HP eradication	alive	Positive	Jung JG et. al. Korean J Gastroenterol 2013;62:117

ND, not described. Resec, Resection. RT, Radiation

MALT lymphoma has been reported to occur in sites with chronic inflammation, i.e., the stomach and salivary and thyroid glands. According to the evidence, primary esophageal MALT lymphoma might also be associated with some type of inflammation. However, the relationship between esophageal MALT lymphoma and local inflammation remains unclear. HP is reported to be associated with an increased risk of gastric malignancies and a decreased risk of esophageal adenocarcinoma [4]. HP infection in the esophagus was reported in Barrett's esophagus and squamous cell carcinoma [5,6]. Although it remains unclear whether HP infection is associated with the pathogenesis of primary esophageal MALT lymphoma, MALT within Barrett's esophagus was associated with esophageal HP infection in 57% of cases and gastric HP infection in 71%; HP was found in approximately one-third of Barrett's esophagus patients [7]. In our patient, Barrett's esophagus and esophageal HP infection were not observed, but eradication therapy induced complete remission. Although it is not known how non-gastric MALT lymphoma regression is achieved via the elimination of HP infection, previous reports indicated that MALT lymphoma in the rectal and salivary glands showed regression after HP eradication therapy [8,9]. Those reports including ours suggest that HP may be involved in the pathogenesis of non-gastric MALT lymphoma, although the underlying mechanism remains unclear. Furthermore, in our case, the MALT lymphoma resolved after the first round of HP eradication therapy without complete eradication. The first course of therapy decreased the gastric HP bacterial load as detected by the pathological findings, suggesting that the effect of HP requires a certain level of bacterial burden [10]. To elucidate the mechanism of occurrence of primary esophageal MALT lymphoma, it will be important to accumulate more information on and to investigate those patients.

Chronic immunosuppression has been reported to be linked with PEL [11]. Several patients with concomitant PEL and HIV infection were reported. Thus, a small portion of the elderly with immunosuppressive conditions may have a tendency to develop MALT lymphoma. Our elderly patient had no HIV infection, no medical history of recurrent infections, and no immunosuppressive condition, and thus some mechanism of localized inflammation including that with HP may be associated with the pathogenesis of esophageal MALT lymphoma.

In summary, our patient with primary esophageal MALT lymphoma achieved complete remission after HP eradication therapy, although without complete eradication. After the second successful round of eradication therapy, she has remained in complete remission for more than 3 years. Although other possibilities such as spontaneous remission must be considered, HP eradication therapy may be correlated with remission of MALT lymphoma. HP eradication therapy may be a potential treatment option for esophageal MALT lymphoma patients with HP infection.

Conflict of interest

The authors declare that they have no conflict of interest.

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