



Primary Esophageal Mucosa-associated Lymphoid Tissue Lymphoma: A Rare Case Report and Review of Other Published Data

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The gastrointestinal tract is the most common extranodal site for lymphomas, and mucosa-associated lymphoid tissue lymphoma is the second most common histological lymphoma subtype. However, primary esophageal mucosa-associated lymphoid tissue lymphomas are extremely rare. Few such cases are documented, and the reports demonstrate inconsistent diagnostic and therapeutic strategies. Herein, a 54-year-old man was referred to our hospital for treatment of dysphagia. Esophagogastroduodenoscopy revealed a large, horseshoe-shaped subepithelial mass in the upper esophagus. Endoscopic ultrasonography and computed tomography revealed that the mass was well-demarcated and confined to the muscularis mucosa, with no abnormalities in other organs or lymph nodes. The mass was presumptively diagnosed as benign, and the patient underwent endoscopic mucosal dissection for pathological confirmation and symptom relief. Pathological examination of the dissection specimen revealed that it was a primary esophageal mucosa-associated lymphoid tissue lymphoma. As the patient had an elevated immunoglobulin G level and *Helicobacter pylori* infection, we administered adjuvant eradication therapy. The patient remains under surveillance and is free of lymphoma recurrence 36 months postoperatively. This case report demonstrates that endoscopic resection and *H. pylori* eradication are effective treatment strategies for early-stage esophageal mucosa-associated lymphoid tissue lymphoma. (Korean J Helicobacter Up Gastrointest Res 2023;23:207-213)

Key Words: Endoscopic submucosal dissection; Esophagus; Lymphoma, B-cell, marginal zone

INTRODUCTION

The gastrointestinal tract is the most common site of extranodal lymphoma involvement. It most often occurs in the stomach, whereas primary esophageal lymphoma is extremely rare, accounting for less than 1% of all primary gastrointestinal lymphomas.¹ Due to its rarity, a standard diagnostic approach and an optimal treatment regimen are yet to be established. In the last decade, there have been only a few case reports on endoscopic submucosal dissection (ESD) as a curative option for primary esophageal mucosa-associated lymphoid tissue lymphoma (PEML) in its early stages.^{2,5} This indication has not been validated due to poorly accumulated data. Herein, we present another case of PEML in which a large-sized mass was treated with ESD and a review of previous reports.

CASE REPORT

A 54-year-old man was referred to our hospital from a local clinic to evaluate an esophageal subepithelial tumor. The patient complained of pain while swallowing solid food and associated epigastric discomfort that started 6 months prior and gradually worsened. He had hypertension, diabetes mellitus, and a history of bladder cancer and had undergone curative partial cystectomy 2 years earlier. During regular follow-ups, no evidence of cancer recurrence was observed. Physical examination revealed no abnormalities, and the peripheral lymph nodes were not palpable. Laboratory data were within normal ranges, including complete blood count, liver, and kidney function test results, CA 19-9 levels, and CEA levels. Esophagogastroduodenoscopy (EGD; GIF H290, Olympus, Tokyo, Japan) revealed a smooth-surfaced, large-sized, longitudinally extended, horseshoe-shaped subepithelial lesion 23 cm from the incisor (Fig. 1A). Gastroesophageal reflux disease with LA-A (Los Angeles classification) was observed at the esophageal-gastric junction, and there was no abnormality in the stomach, except for atrophic gastritis C-II

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(Kimura-Takemoto classification). EUS (UM-2R, Olympus) revealed a well-demarcated hypoechoic mass confined to the muscularis mucosal layer (Fig. 1B). Computed tomography (CT) revealed a poorly enhanced, eccentric, and asymmetric wall thickening with intraluminal narrowing of the upper esophagus. No other organs were involved, including the liver, spleen, or lymph nodes (Fig. 1C).

The initial presumptive diagnosis was a benign tumor, such as leiomyoma; however, tumor resection was required to relieve the patient's dysphagia. Considering the comorbidities associated with esophagectomy, endoscopic resection was selected as the option for coincidental tumor resection and a confirmative diagnosis. Given its well-known advantages in terms of higher en-bloc

resection rates and lower recurrence rates than endoscopic mucosal resection (EMR), we performed ESD in the present case.

After informed consent was obtained from the patient, ESD was performed under conscious sedation induced by propofol (120 mg) and midazolam (2 mg). The incision site was marked with a J knife, and submucosal injection was performed using a normal saline solution combined with 1:10,000 epinephrine and indigo carmine. After 360-degree precutting with a J knife, the submucosal layer was dissected using a J knife. The tumor was resected without any adverse events (Fig. 2A). The en bloc specimen was 6.1×2.3×0.9 cm in size, and the tumor itself measured across 5.7×2.0 cm (Fig. 2B).

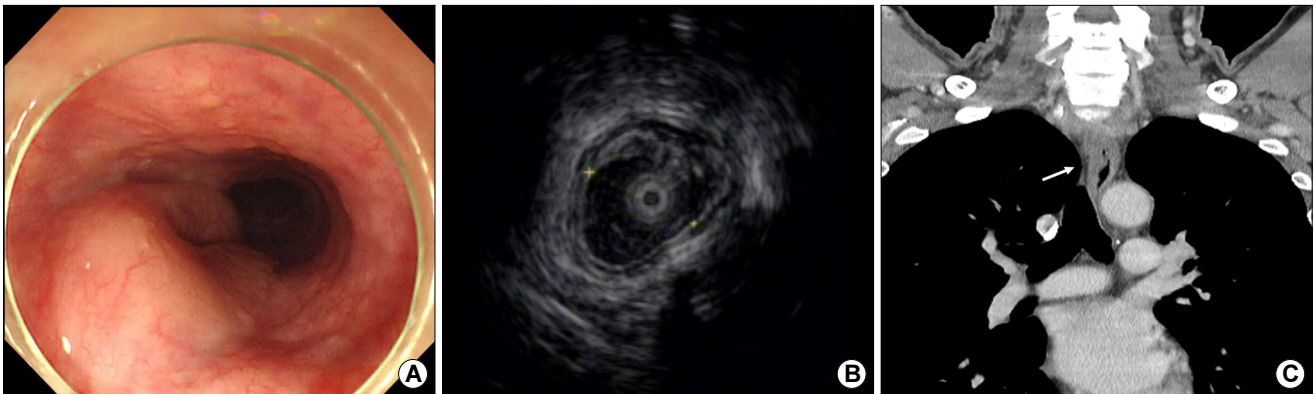


Fig. 1. Initial work-up images. (A) Esophagogastroduodenoscopy revealed a horseshoe-shaped subepithelial tumor with a smooth surface protruding into the lumen of the esophagus, 23 cm from the incisor. (B) EUS revealed a well-demarcated hypoechoic lesion confined within the deep mucosal layer. (C) Chest computed tomography scanning showed poorly enhanced, eccentric, and asymmetric wall thickening (white arrow) in the upper esophagus.

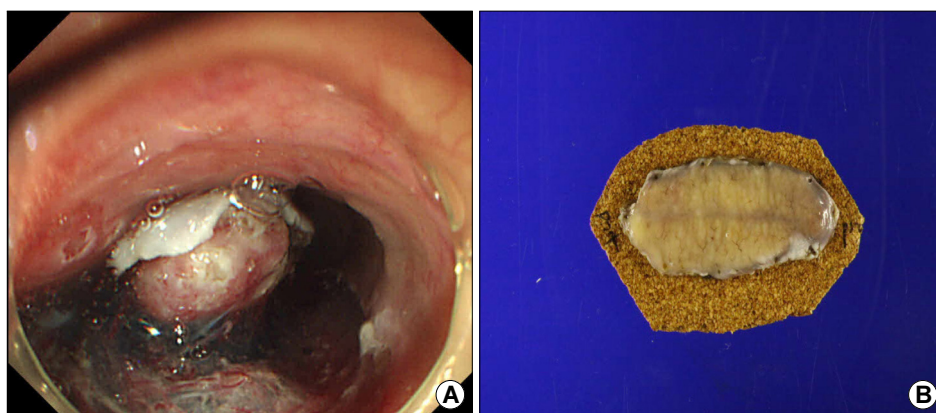


Fig. 2. Endoscopic images during submucosal dissection. (A) The tumor was resected en bloc, with no postoperative complications. (B) The gross specimen, a well-circumscribed yellowish tumor measuring 5.7×2.0 cm.

Pathological examination revealed that small lymphocytes with irregular nuclei had heavily infiltrated and expanded the interfollicular zones, leaving small remnant germinal centers. Immunohistochemically, these atypical lymphoid cells stained positive for clusters of differentiation (CD) 20 and BCL-2; however, they were negative for CD5, CD10, CD23, cyclin D1, and BCL-6 (Fig. 3). Because there was no evidence of lymphoma involvement at other sites, the patient was diagnosed with PEML, based on these pathological features. The resected specimen margins were free of lymphoma infiltration. A follow-up endoscopy was performed the following day. Only a

clean-based ulcer was present; therefore, the patient started swallowing water. On the second day post-ESD, the patient was tested on a soft diet for tolerability and was discharged. Three months after ESD, the patient's dysphagia and epigastric discomfort resolved. EGD showed only a scar change at the resection site. The patient was treated with *Helicobacter pylori* eradication because of an elevated IgG level for *H. pylori* (13.9 U/mL). The patient has been under regular surveillance for 3 years and has remained recurrence-free.

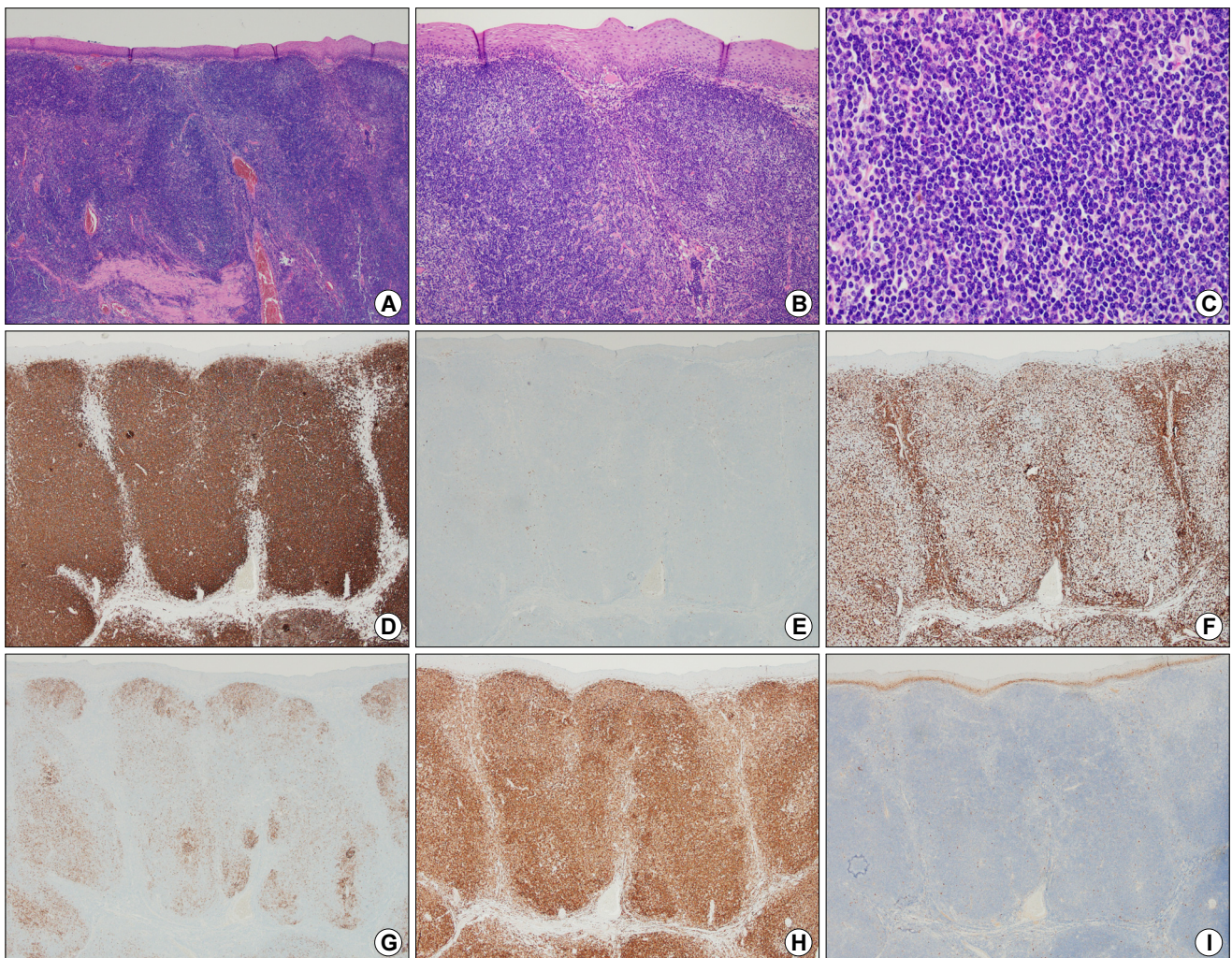


Fig. 3. Pathological examination of the resected tumor. (A-C) Hematoxylin and eosin (H&E) staining revealed small lymphoma cells heavily infiltrating the preserved mantle in the marginal zone of the germinal center. Lymphoepithelial lesions are not conspicuous via H&E staining (A: $\times 40$, B: $\times 100$, C: $\times 400$). (D-I) Immunohistochemically, the specimen was positive for CD20 (D) and BCL-2 (H) but negative for CD10 (E), CD5 (F), CD23 (G), and cyclin D1 (I) (immunohistochemistry, $\times 40$).

DISCUSSION

Gastrointestinal lymphoma has two prevalent histological subtypes: diffuse large B-cell lymphoma and mucosa-associated lymphoid tissue (MALT) lymphoma.⁶ The latter is a low-grade mature B-cell lymphoma that originates from acquired MALT due to a chronic inflammatory stimulus. Thus, MALT lymphoma can arise at any site ordinarily devoid of lymphoid tissue; however, the esophagus is a very rare site of occurrence.⁷ A recent study observed a geographically different prevalence. Unlike in the USA, where diffuse large B-cell lymphoma is the most prevalent, the MALT type is Asia's most frequent primary esophageal lymphoma.⁸

There is no authorized treatment regimen for PEML. The initial treatments for PEML have varied, including surgery, chemotherapy, radiation, *H. pylori* eradication, EMR, and ESD.^{3,8} Generally, MALT lymphomas exhibit indolent characteristic by growing and spreading slowly. Therefore, endoscopic resection or *H. pylori* eradication could be a less invasive and effective curative treatment

option for localized PEML. Table 1 shows that there have been 11 case reports of PEML treated with endoscopic removal and/or *H. pylori* eradication as a first-line treatment in the English literature. To the best of our knowledge, most of these cases (n=9) were clinically classified as stage I when the Lugano system was used.

Among the 11 cases, the initial treatments for PEML included EMR (n=3), ESD (n=4), and *H. pylori* eradication (n=4). Similar to our case, PEMLs present as subepithelial tumors in all cases. When visualizing PEML with light endoscopy, it is usually described as a soft subepithelial nodule, fold, or ridge covered by smooth normal mucosa. These tumors tend to extend longitudinally in the cranio-caudal direction and are often accompanied by central indentations as they grow; this has already been suggested as a cardinal feature of PEML's gross appearance.⁹

Notably, several methods used for further evaluation in clinical practice are insufficient for detecting PEML. The EUS findings of PEML tends to be nonspecific. PEML usually presents as a well-demarcated subepithelial tumor originating in the muscular mucosa or submucosal layer.

Table 1. Summary of the Reported Cases of Primary Esophageal Mucosa-associated Lymphoid Tissue Lymphoma

| No. | Age (years) | Sex | Stage ^a | Location | Size (cm) | HP infection ^b | Diagnostic method | Pre-treatment pathologic confirmation | Treatment | Follow-up period (mo) | Outcome | Reference |
|--------------|-------------|-----|--------------------|----------|--------------------|---------------------------|-------------------|---------------------------------------|------------------------------|-----------------------|---------|-------------------------------|
| Present case | 54 | M | I | U | 5.7×2 | + | ESD | No | ESD, HP eradication | 36 | CR | |
| 1 | 66 | M | I | L | 1.5×0.5 | - | ESD | No | ESD | 12 | CR | Kudo et al. ² |
| 2 | 69 | F | I | M | 2 | - | Biopsy | Yes | ESD | 57 | CR | Kobayashi et al. ³ |
| 3 | 77 | F | I | L | 4.5×2.8×1.5 | - | ESD | No | ESD | 5 | CR | Xia et al. ⁴ |
| 4 | 56 | F | I | M to L | NA | + | ESD | No | ESD, HP eradication | NA | CR | Ling et al. ⁵ |
| 5 | 83 | F | I | U | NA | - | EMR | No | EMR | 22 | CR | Hosaka et al. ¹⁰ |
| 6 | 59 | F | I | U | 1.4×0.9 | - | EMR | No | EMR | 24 | CR | Baek et al. ¹¹ |
| 7 | 70 | F | I | M | 0.6×0.4 2.0×0.8 | - | Biopsy | Yes | EMR, radiotherapy | 36 | CR | Yano et al. ¹² |
| 8 | 44 | M | I | L | 0.8 | NA | Biopsy | Yes | HP eradication | 12 | CR | Sawada et al. ¹⁷ |
| 9 | 76 | F | I | L | 2 | + | Biopsy | Yes | HP eradication | 36 | CR | Moriya et al. ¹⁸ |
| 10 | 50 | F | II | U to L | NA | + | Biopsy | Yes | HP eradication, chemotherapy | 20 | PR | Takeuchi et al. ¹⁹ |
| 11 | 70 | M | IV | U | 5 | + | Biopsy | Yes | HP eradication, chemotherapy | 6 | PR | Tsujii et al. ²⁰ |

U, upper; M, middle; L, lower; EMR, endoscopic mucosal resection; ESD, endoscopic submucosal dissection; HP, *Helicobacter pylori*; CR, complete remission; PR, partial remission; NA, not available.

^aStaging was performed using the Lugano system.

^bHP infection was defined as any positive finding on the rapid urease test, 13C urea breath test, serum IgG, or tissue specimen.

In fact, most are hypoechoic; however, they can have focal iso-, hyper-, or variable echogenicity. Leiomyoma, gastrointestinal stromal tumors, and granular cell tumors can also present similar features, requiring differential diagnosis. For these reasons, EUS is more favorable than a differential diagnosis for assessing the depth of invasion and detecting regional lymph node involvement. The CT findings were also non-diagnostic. PEML has generally been reported as a weakly contrast-enhanced mass;⁹ however, small masses show only wall thickening and luminal strictures, leading to confusion with esophageal carcinoma.

It is essential but challenging to confirm the diagnosis of PEML due to its subepithelial localization. In 5 (45.5%) of the 11 reported cases, specimens were obtained before the patients were treated. All the 5 cases were diagnosed using standard forceps biopsy. The remaining 6 cases were diagnosed after endoscopic resection.

Since the first reported case in 2014, seven cases of PEML have been treated with EMR¹⁰⁻¹² and ESD^{2,5} for which detailed data are available. The masses removed using EMR were all ≤ 2 cm in size. The masses removed by ESD were measured to be 1.5×0.5 cm, 2.8×1.5 cm, 2×4.3 cm, and unmeasured. They were confined to the deep mucosa or submucosa, and no evidence of metastatic lymph nodes was observed upon CT or EUS examinations. Subsequently, all patients achieved complete resection and were recurrence-free during follow-up. In the present case, we resected a large mass (5.7×2 cm) with ESD, and the patient remains alive to date without recurrence for 3 years. This is the largest-sized mass among the PEML cases presented in Table 1. This indolent malignancy is usually well-demarcated and less invasive; therefore, larger tumors can be resected entirely and more easily than other invasive malignancies if the endoscopist is experienced.

It is well known that *H. pylori* infection contributes to gastric MALT lymphoma.^{13,14} However, unlike gastric MALT lymphoma, the association between PEML and *H. pylori* infection remains unclear. Four (36.3%) of the 11 reported cases were positive for *H. pylori* infection. This is lower than the prevalence of 70~80% for *H. pylori* infection in gastric MALT lymphoma and even lower than the prevalence of 50~70% reported for the general population of

East Asia.^{15,16} Among the 11 cases, two small (<2 cm) tumors in the distal esophagus treated with solitary *H. pylori* eradication achieved complete remission within 1 and 3 years of follow-up.^{17,18} In contrast, two other patients treated with *H. pylori* eradication as the first-line therapy showed partial or no responses; however, these were staged as stage II or IV.^{19,20} In our case, the patient's IgG level was elevated due to *H. pylori* infection; therefore, we performed additional *H. pylori* eradication as an adjuvant treatment following curative resection.

Although the relationship between PEML and *H. pylori* remains uncertain, we believe that eradicating *H. pylori* as an initial or adjuvant treatment can be beneficial. This is because there have been reported cases of PEML in which complete remission was achieved through *H. pylori* eradication.^{17,18} Hence, it is important to not exclude the possibility of an association between PEML and *H. pylori*. Furthermore, *H. pylori* eradication is advantageous due to its low cost and its being nearly harmless to the patient. However, it appears to be challenging to achieve complete remission in advanced stages of PEML through *H. pylori* treatment alone,^{19,20} suggesting the need for additional treatment alongside *H. pylori* eradication. The effectiveness of *H. pylori* eradication in PEML requires further verification.

Since the risk factors for PEML are still unclear, it is speculated that chronic inflammatory stimulation from acid reflux, hot water, chemicals, and other infections could be a potential trigger factor in addition to *H. pylori* infection.^{3,4} However, the previously published cases shown in Table 1 did not report any accompanying esophageal abnormality. In our case, the presence of reflux esophagitis (LA-A, Los Angeles classification) suggests a potential link between chronic inflammatory stimulation and the development of PEML.

In summary, we successfully treated a patient with PEML using ESD and *H. pylori* eradication therapy, and the patient did not experience recurrence for 3 years after ESD. Therefore, endoscopic resection and adjuvant *H. pylori* eradication may be preferred for single localized masses. As the clinical profile of PEML is not yet clear, and there is no established treatment, further accumulation of data and additional research are needed for this disease.

AVAILABILITY OF DATA AND MATERIAL

The datasets generated or analyzed during the study are available from the corresponding author on reasonable request.

CONFLICT OF INTEREST

There is no potential conflict of interest related to this work.

AUTHOR CONTRIBUTIONS

Conceptualization: Seung Han Kim. Data curation: Ji Hea Bang. Formal analysis: Jin Hyong Kang. Funding acquisition: Seung Han Kim. Investigation: Jin Hyong Kang. Methodology: Tae Sung Jeon. Project administration: Seung Han Kim. Resources: Ji Hea Bang. Software: Jin Hyong Kang. Supervision: Jong Jae Park. Validation: Moon Kyung Joo. Visualization: Beom Jae Lee. Writing - original draft: Ji Hea Bang. Writing - review & editing: Seung Han Kim.

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