Internal Medicine
The Japanese Society of Internal Medicine
doi: 10.2169/internalmedicine.0487-17
Intern Med 57: 2347-2352, 2018
http://internmed.jp

【 CASE REPORT 】

Primary Localized Esophageal Mucosa-associated Lymphoid Tissue Lymphoma Treated by Endoscopic Submucosal Dissection

Sayo Kobayashi[1,2], Masaya Iwamuro[1], Kenji Nishida[3], Takehiro Tanaka[4], Seiji Kawano[1], Yoshiro Kawahara[5], Tadashi Yoshino[3] and Hiroyuki Okada[1]

Abstract:
A 69-year-old Japanese woman presented to our hospital for the further investigation of an esophageal subepithelial tumor. A diagnosis of extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma) was made by an endoscopic biopsy. The patient had no involvement other than the esophagus. The tumor was resected using endoscopic submucosal dissection. Lymphoma recurrence has not been documented in the 57 months since resection. This case suggests that although a detailed preoperative evaluation is required to determine the extent of tumor, endoscopic resection may be an option for the long-term disease control of MALT lymphoma of the esophagus.

Key words: esophageal neoplasms, mucosa-associated lymphoid tissue (MALT) lymphoma, non-Hodgkin lymphoma, endoscopic submucosal dissection

(Intern Med 57: 2347-2352, 2018)
(DOI: 10.2169/internalmedicine.0487-17)

Introduction

Extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma) is one of the most common non-Hodgkin lymphomas arising in the gastrointestinal tract (1). This lymphoma affects other tissues or organs outside of the lymph nodes, such as the thyroid, ocular adnexa, lungs, salivary glands, liver, and skin (2, 3). In the gastrointestinal tract, the stomach is the most frequently identified primary site, whereas esophageal involvement is rare. To date, only 22 cases of esophageal MALT lymphoma have been reported in the English medical literature (4-25). Due to the rarity of esophageal MALT lymphomas, an appropriate treatment strategy has not yet been established.

We encountered a patient with primary localized MALT lymphoma in the esophagus that was successfully resected by endoscopic submucosal dissection. Lymphoma recurrence has not been documented in the 57 months since resection. In this report, we review previously reported cases of this disease and focus mainly on the characteristics, treatment, and outcome.

Case Report

A 69-year-old Japanese woman underwent esophagogastroduodenoscopy during a routine medical checkup, and a subepithelial tumor was identified in the esophagus. The patient did not undergo other examinations at that time. Esophagogastroduodenoscopy performed two years later revealed that the esophageal tumor had increased in size. The patient was referred to our hospital for the further investigation of the esophageal lesion. The patient had been taking nifedipine and magnesium oxide for hypertension and constipation. She underwent resection of atheroma in the neck at 61 years of age. At 67 years of age, the patient underwent

[1]Department of Gastroenterology and Hepatology, Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, Japan, [2]Department of Internal Medicine, Fukuyama City Hospital, Japan, [3]Department of Pathology, Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, Japan, [4]Department of Pathology, Okayama University Hospital, Japan and [5]Department of Endoscopy, Okayama University Hospital, Japan
Received: November 6, 2017; Accepted: January 12, 2018; Advance Publication by J-STAGE: March 30, 2018
Correspondence to Dr. Masaya Iwamuro, iwamuromasaya@yahoo.co.jp

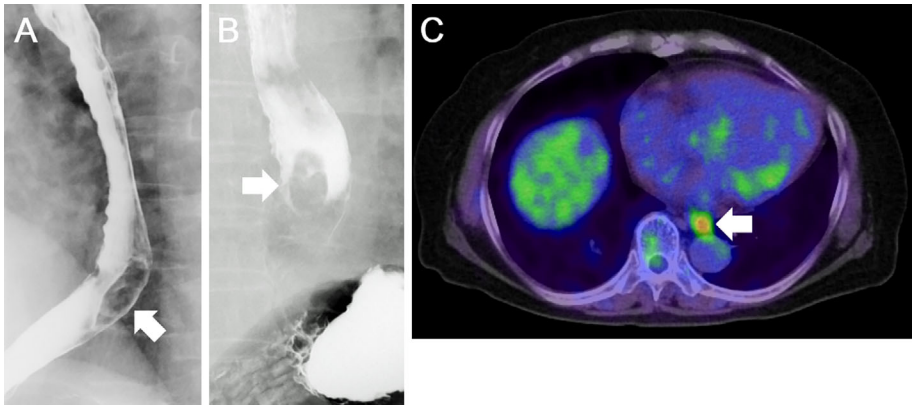

Figure 1. **Fluoroscopy and positron emission tomography images. Barium follow-through shows a round, elevated lesion in the middle of the esophagus (A, B). The tracer uptake is noted only in the esophagus on positron emission tomography (C).**

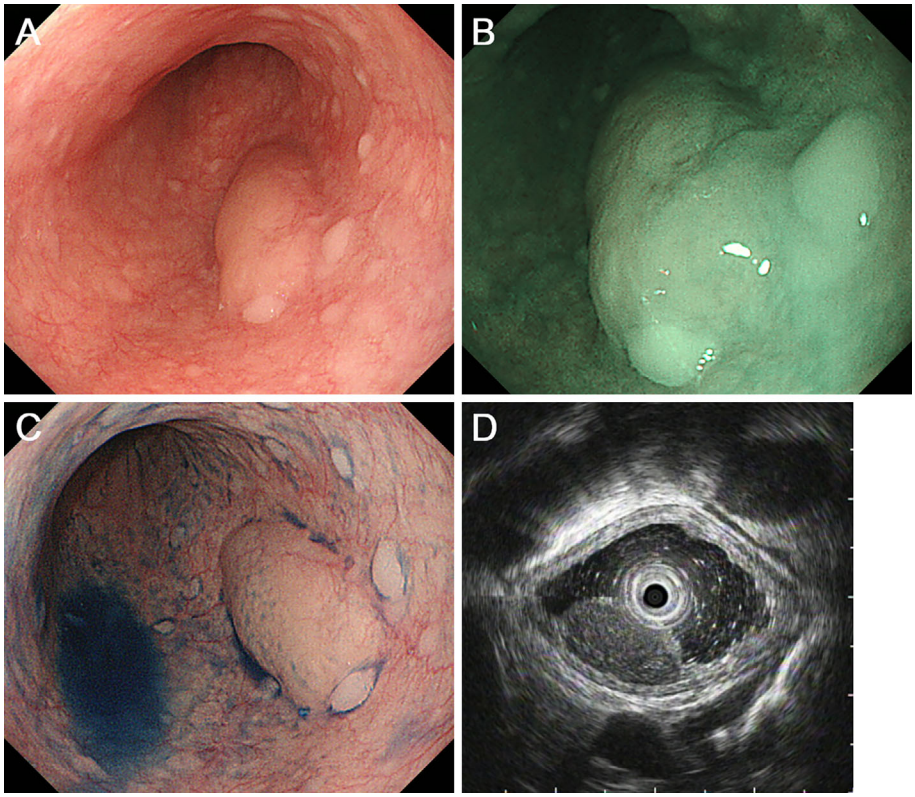

Figure 2. **Esophagogastroduodenoscopy images. A solitary subepithelial tumor is shown on white light (A) and narrow band imaging (B). The tumor is emphasized after indigo carmine spraying (C). Endoscopic ultrasonography shows a homogenous, hypoechoic tumor (D).**

surgical resection of colon cancer, and it was curatively resected. She had been treated for Hashimoto's thyroiditis since 70 years of age. The patient had no history of esophageal or gastroduodenal disease. A physical examination revealed no abnormalities, and there were no lymphadenopathies. The laboratory findings, including hemoglobin, lactate dehydrogenase, and soluble interleukin-2 receptor levels, were within the normal range, except for the thyroglobulin levels, which were elevated (80.79 ng/mL, normal range: 0.0-32.7 ng/mL). The patient tested negative for *Helicobacter pylori* infection serologically and pathologically. A urea breath test result was also negative.

Barium follow-through showed a round, elevated lesion that was covered with smooth mucosa in the middle of the esophagus (Fig. 1A and B). On ^{18}F-fluorodeoxyglucose positron emission tomography, the tracer uptake was noted only in the esophagus (Fig. 1C). There were no lymphadenopathies on computed tomography. Esophagogastroduodenoscopy revealed a solitary subepithelial tumor, approximately 20 mm in diameter (Fig. 2A: white light image, 2B: narrow band imaging, 2C: post-indigo carmine spraying). Endoscopic ultrasonography showed a homogenous, hypoechoic

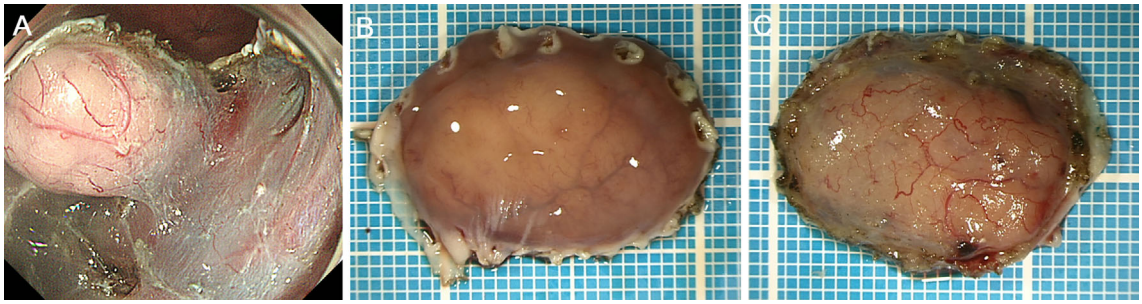

Figure 3. **Images during endoscopic submucosal dissection. En bloc resection is performed without any procedure-related adverse events (A). On the external surface (B) and the cut surface (C), dilated microvasculature is observed.**

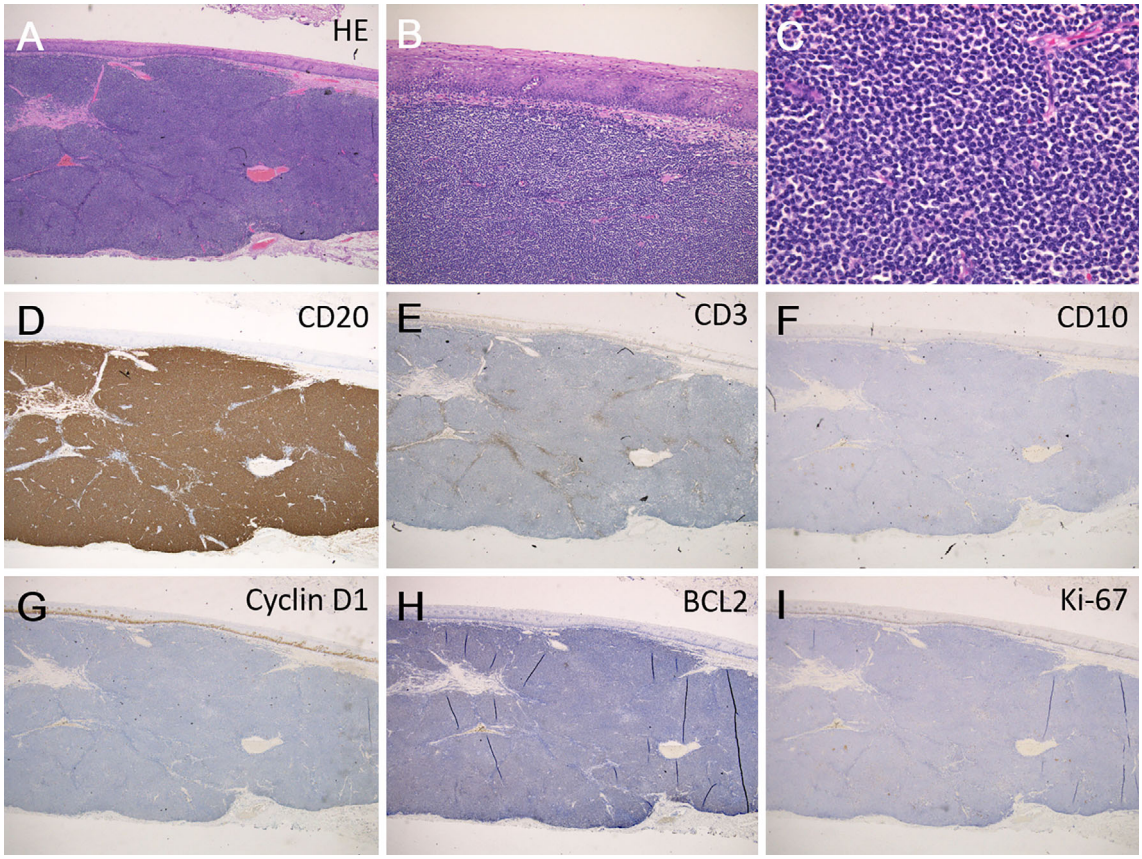

Figure 4. **Pathological images of the resected specimen. Infiltration of small to medium-sized lymphoid cells are seen in Hematoxylin and Eosin staining (A: ×2, B: ×4, C: ×40). The stratified squamous epithelium of the esophagus is intact (B). Lymphoma cells are positive for CD20 (D: ×2); negative for CD3 (E: ×2), CD10 (F: ×2), and cyclin D1 (G: ×2); and weakly positive for BCL2 (H: ×2). The percentage of tumor cells positive for Ki-67 staining is less than 1% (I: ×2).**

tumor located within the second and third layers of the esophagus (Fig. 2D). A diagnosis of MALT lymphoma was made based on a pathological analysis of the biopsied specimen taken from the esophageal lesion. Lymphoma involvement was not detected during colonoscopy. Consequently, we diagnosed the tumor as primary localized esophageal MALT lymphoma. The esophageal lesion was resected using endoscopic submucosal dissection (Fig. 3). There were no adverse procedure-related events during or after the surgery.

A pathological analysis of the resected specimen revealed infiltration of small to medium-sized lymphoid cells exhibiting a vague nodular pattern (Fig. 4A). Neoplastic cells existed in the lamina propria to the submucosal layers, and the stratified squamous epithelium of the esophagus was intact (Fig. 4B and C). Immunohistochemical studies revealed that the lymphoid cells were positive for CD20 (Fig. 4D), negative for CD3 (Fig. 4E), CD10 (Fig. 4F), and cyclin D1 (Fig. 4G), and weakly positive for BCL2 (Fig. 4H). The percentage of tumor cells positive for Ki-67 staining was less than 1%, indicating few mitotic cells (Fig. 4I). The diagno-

Table. Characteristics of the Previously Reported Cases of Esophageal MALT Lymphoma.

Reference	Age (years)	Sex	Stage* (involved sites other than the esophagus)	Site	Gross appearance	Treatment	Follow-up period	Outcome
5	63	F	I	Middle to lower	Sessile SET	NA	NA	NA
6	83	F	I	Upper	Sessile SET	EMR	22 months	Alive without disease
7	74	M	I	Middle	Sessile SET	EMR, radiation	NA	Alive without disease
9	49	M	I	Lower	Sessile SET	Surgical resection	1 year	Alive without disease
11	70	F	I	Middle	Sessile SET	EMR, radiation	3 years	Alive without disease
12	44	M	I	Lower	Sessile SET	HP eradication	1 year	Alive without disease
14	59	F	I	Upper	Sessile SET	ESD	2 years	Alive without disease
15	59	M	I	Upper to lower	Sessile SET	EMR, radiation	3 years	Alive without disease
17	37	M	I	Middle to lower	Chronic ulcer	Radiation, rituximab	3 years	Alive without disease
19	50	M	I	Middle	Semipedunculated SET	Surgical resection	12 months	Alive without disease
20	66	M	I	Lower	Sessile SET	ESD	1 year	Alive without disease
21	56	F	I	Middle to lower	Sessile SET	ESD, HP eradication	NA	Alive without disease
24	76	F	I	Lower	Sessile SET	HP eradication	3 years	Alive without disease
25	75	M	I	Middle to lower	Sessile SET	Surgical resection	8 months	Alive without disease
4	61	M	I (stomach)	Upper	Sessile SET	Chemotherapy	NA	NA
23	53	M	I–IV (stomach, lung)**	Middle	Sessile SET	Surgical resection, radiation, HP eradication, chemotherapy	12 months	Alive without disease
22	49	M	II_2 (abdominal and pelvic LNs)	Middle	Sessile SET	Chemotherapy	6 months	Alive without disease
10	65	M	IV (lung, paraesophageal LNs)	Upper	Sessile SET	Chemotherapy	2 years	Alive, unknown lymphoma status
18	70	M	IV (mediastinal LNs)	Upper	Sessile SET	HP eradication, rituximab	6 months	Alive with disease
8	61	M	IV (paraseptal and aortopulmonary window LNs)	Middle to lower	Sessile SET	Surgical resection, HP eradication	NA	NA
16	60	F	IV (pharyngeal LNs)	Upper to lower	Sessile SET	Chemotherapy with rituximab	NA	Alive without disease
13	62	F	IV (stomach, lung)	Upper to lower	Sessile SET	Chemotherapy with rituximab	NA	Alive with disease
Present case	69	F	I	Middle	Sessile SET	ESD	57 months	Alive without disease

*Lugano staging system for gastrointestinal lymphoma, **Stage I at the initial diagnosis and subsequently progressed to stage IV.

MALT: mucosa-associated lymphoid tissue, SET: subepithelial tumor, NA: not available, EMR: endoscopic mucosal resection, HP: *Helicobacter pylori*, ESD: endoscopic submucosal dissection, LN: lymph nodes

sis of esophageal MALT lymphoma was confirmed based on these pathological features. The margin was negative on the resected specimen, suggesting that all lymphoma cells in the esophagus had been removed. After endoscopic resection, physical, blood count, and routine chemistry tests; esophagogastroduodenoscopy; computed tomography; and 18F-fluorodeoxyglucose positron emission tomography were performed every six months for two years and subsequently once a year. No recurrence had been documented in the 57 months since resection.

Discussion

Lymphoma arising in the esophagus is quite uncommon, comprising less than 1% of primary gastrointestinal lymphomas (26). Primary esophageal lymphoma varies from MALT lymphoma, diffuse large B cell lymphoma, and other infrequent pathological subtypes, such as B cell, T cell, or NK cell lymphomas and Hodgkin lymphoma (24). Moriya et al. reviewed previously reported cases of stage I primary esophageal lymphoma and found that 12 of the 37 cases (32.4%) were MALT lymphoma (24).

To our knowledge, 22 cases of MALT lymphoma involving the esophagus have been reported to date (Table). These were 14 men and 8 women, and the median age at the lymphoma diagnosis was 61 years, ranging from 37 to 83 years. Six patients showed no symptoms before undergoing esophagogastroduodenoscopy, whereas 13 had some gastrointestinal symptoms that may or may not have been associated with the esophageal lesion. Symptoms described in previous reports include dysphagia (n=6), heartburn (n=3), melena (n=1), hematochezia (n=1), and hematemesis (n=1).

The median diameter of esophageal MALT lymphoma was 27.5 mm among the cases in which the sizes were mentioned. However, in some cases, the lymphoma lesion extended from the upper esophagus to the lower esophagus, and the exact tumor size was not reported. The middle third of the esophagus was predominantly affected (n=13), followed by the lower (n=12) and upper (n=8) thirds.

In the stomach, *H. pylori* is believed to be involved in the emergence of gastric MALT and lymphomagenesis in most cases with MALT lymphoma (27). Therefore, early-stage gastric MALT lymphoma can regress after therapeutic reversal of the chronic immune stimulus through antibiotic eradication of the *H. pylori* infection. Conversely, there has been only one report in which complete remission of esophageal MALT lymphoma was achieved after *H. pylori* eradication without anti-lymphoma treatment (24). Although Sawada et al. also reported a case wherein esophageal MALT lymphoma disappeared after the administration of lansoprazole, amoxicillin, and clarithromycin for two weeks, the infection status of *H. pylori* was not described in their report (12). We consider the role of *H. pylori* to be limited in the pathogenesis of esophageal MALT lymphoma, since cases negative for *H. pylori* account for 38.9% of the previously reported cases (7 of 18 patients). The present case tested negative for *H. pylori* as well. Other possible causes for a chronic antigenic stimulus followed by acquired MALT formation and lymphomagenesis in the esophagus include esophagitis due to acid reflux, bile reflux, and eosinophilic infiltration. However, the involvement of esophagitis has been described in only a few reports (4). Mechanisms underlying the growth and development of esophageal MALT lymphoma should be investigated in the future.

Morphologically, all but one case of MALT lymphoma of the esophagus reportedly presented with either a single tumor or multiple subepithelial tumors. The one case reported by Malik et al. that showed an ulcerative lesion was the only exception (17). However, our previous study investigating 146 cases with gastric MALT lymphoma revealed gastric lesions that presented as erosions/ulcers (30.1%), whitish mucosa (28.8%), cobblestone appearance (11.6%), early gastric cancer-like lesions (6.8%), and mixed lesions (2.7%), whereas 19.9% of the cases showed subepithelial tumors (28). Thus, the macroscopic features are diverse in gastric MALT lymphomas, whereas esophageal MALT lymphomas predominantly present as subepithelial tumors. The different typical morphologies between esophageal and gastric MALT lymphomas may reflect the different pathogenesis of acquired MALT in these organs, as described above. Whatever its pathogenesis, esophageal MALT lymphoma must be differentiated from other subepithelial tumors, such as leiomyomas and granular cell tumors (29).

A pathological analysis is essential for the diagnosis of lymphomas. In the current patient, the diagnosis of esophageal MALT lymphoma was made based on the pathological analysis of the endoscopically biopsied specimens. Ten of the 22 reported cases with esophageal MALT lymphoma were diagnosed using a conventional biopsy during esophagogastroduodenoscopy as well. Five cases were diagnosed after surgical resection of the esophageal tumor (8, 9, 19, 23, 25). Other procedures include endoscopic mucosal resection (n=3) (7, 14, 15), endoscopic ultrasound-guided fine needle aspiration (n=2) (13, 16), a stacked forceps biopsy (n=1) (22), and endoscopic submucosal dissection (n=1) (21). Physicians can opt to use these methods when they are unable to obtain adequate specimens using a conventional biopsy.

The clinical stages of primary gastrointestinal lymphoma using the Lugano system staging (30) were stage I (n=16) in most of the previously reported cases. Lymphoma was localized in the esophagus in 15 cases, and the remaining patient had involvement of the stomach (4). In patients with localized disease, esophageal MALT lymphoma can be curatively removed by surgical resection (9, 19, 25) or endoscopic resection (6, 14, 20), as shown in our present patient. Previous studies have demonstrated that endoscopic resection alone resulted in complete remission for 1 year, 22 months, and 2 years after resection. Our patient has been disease-free for 57 months since endoscopic submucosal dissection. The clinical course of our case underscores the notion that local excision is probably sufficient for the long-term disease control of primary localized esophageal MALT lymphoma. Radiation is a treatment of choice for large lesions (15).

Previous studies reported one case with esophageal MALT lymphoma in stage II_2 and five cases in stage IV (8, 10, 13, 16, 18, 22). These patients had involvement of the lung (n=2) and stomach (n=1) (10, 13), in addition to the pharyngeal, mediastinal, intraabdominal, and pelvic lymph nodes. Generally, rituximab-containing chemotherapy regimens are administered for advanced-stage MALT lymphoma. Of note, in one patient, recurrence was detected in the stomach and lung 21 months after resection of localized esophageal MALT lymphoma (23). Therefore, gastroenterologists should be alert for the emergence of lymphoma involvement in the lung and stomach when monitoring disease relapse or progression in patients with esophageal MALT lymphoma.

In conclusion, we treated a patient with MALT lymphoma in the esophagus by endoscopic submucosal dissection. No recurrence has been documented in the 57 months since resection. Although there is no doubt that a detailed preoperative evaluation of the extent of lymphoma is mandatory, endoscopic resection may be an option for the long-term disease control of primary localized esophageal MALT lymphoma.

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

References

1. Isaacson PG, Chott A, Nakamura S, Muller-Hermelink HK, Harris NL, Swerdlow SH. Extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma). In: WHO

Classification of Tumours of Haematopoietic and Lymphoid Tissues. 4th ed. Swerdlow SH, Campo E, Harris NL, Jaffe ES, Pileri SA, Stein H, Eds. IARC, Lyon, 2008: 214-217.
2. Raderer M, Kiesewetter B, Ferreri AJ. Clinicopathologic characteristics and treatment of marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma). CA Cancer J Clin **66**: 153-171, 2016.
3. Matutes E, Montalban C. Clinical features and management of non-gastrointestinal non-ocular extranodal mucosa associated lymphoid tissue (ENMALT) marginal zone lymphomas. Best Pract Res Clin Haematol **30**: 99-108, 2017.
4. Soweid AM, Zachary PE Jr. Mucosa-associated lymphoid tissue lymphoma of the oesophagus. Lancet **348**: 268, 1996.
5. Nishryama Y, Yamamoto Y, Ono Y, et al. Visualization of esophageal non-Hodgkin's lymphoma with Ga-67 scintigraphy. Ann Nucl Med **13**: 419-421, 1999.
6. Hosaka S, Nakamura N, Akamatsu T, et al. A case of primary low-grade mucosa associated lymphoid tissue (MALT) lymphoma of the esophagus. Gut **51**: 281-284, 2002.
7. Kitamoto Y, Hasegawa M, Ishikawa H, et al. Mucosa-associated lymphoid tissue lymphoma of the esophagus: a case report. J Clin Gastroenterol **36**: 414-416, 2003.
8. Shim CS, Lee JS, Kim JO, et al. A case of primary esophageal B-cell lymphoma of MALT type, presenting as a submucosal tumor. J Korean Med Sci **18**: 120-124, 2003.
9. Miyazaki T, Kato H, Masuda N, et al. Mucosa-associated lymphoid tissue lymphoma of the esophagus: case report and review of the literature. Hepatogastroenterology **51**: 750-753, 2004.
10. Chung JJ, Kim MJ, Kie JH, Kim KW. Mucosa-associated lymphoid tissue lymphoma of the esophagus coexistent with bronchus-associated lymphoid tissue lymphoma of the lung. Yonsei Med J **46**: 562-566, 2005.
11. Yano S, Usui N, Dobashi N, et al. A case of primary esophageal mucosa-associated lymphoid tissue lymphoma with a numerical abnormality of 18q21 detected by fluorescence in situ hybridization. Ann Hematol **88**: 703-704, 2009.
12. Sawada K, Ikuta K, Itabashi K, et al. An unusual elevated lesion of the oesophagus. Gut **60**: 441, 2011.
13. Hayashi M, Ueda K, Tanaka T, et al. Mucosa-associated lymphoid tissue (MALT) lymphoma arising in the esophagus, stomach, and lung. Gen Thorac Cardiovasc Surg **59**: 826-830, 2011.
14. Baek DH, Kim GH, Song GA, et al. Primary esophageal mucosa-associated lymphoid tissue lymphoma treated with endoscopic resection. Gastrointest Endosc **75**: 1282-1283, 2012.
15. Kishi K, Maeda H, Nakamura Y, Shirai S, Sato M. Radiotherapy for mucosa-associated lymphoid tissue (MALT) lymphoma of the esophagus: a case report with a diagnostic and therapeutic discussion. Int J Clin Oncol **17**: 174-180, 2012.
16. Ogura T, Tajika M, Hijioka S, et al. First report of a mucosa-associated lymphoid tissue (MALT) lymphoma of the esophagus diagnosed by endoscopic ultrasound-guided fine-needle aspiration (EUS-FNA). Endoscopy **44**(Suppl 2 UCTN): E167-E168, 2012.
17. Malik AO, Baig Z, Ahmed A, Qureshi N, Malik FN. Extremely rare case of primary esophageal mucous associated lymphoid tissue lymphoma. World J Gastrointest Endosc **5**: 446-449, 2013.
18. Tsujii Y1, Nishida T, Kato M, et al. Mucosa-associated lymphoid tissue (MALT) lymphoma of the esophagus. Dis Esophagus **26**: 349-350, 2013.
19. Bardisi ES, Alghanmi N, Merdad AA. Primary mucosa-associated lymphoid tissue lymphoma of the esophagus masquerading as a benign tumor. Ann Med Surg (Lond) **3**: 39-42, 2014.
20. Kudo K, Ota M, Narumiya K, Shirai Y, Ohki T, Yamamoto M. Primary esophageal mucosa-associated lymphoid tissue lymphoma treated by endoscopic submucosal dissection. Dig Endosc **26**: 478-481, 2014.
21. Ling T, Min H, Zou X. A rare esophageal neoplasm. Gastroenterology **147**: e8-e9, 2014.
22. Lee DS, Ahn YC, Eom DW, Lee SJ. Primary esophageal mucosa-associated lymphoid tissue lymphoma diagnosed by using stacked forceps biopsy. Dis Esophagus **29**: 887-890, 2016.
23. Byun SJ, Kang HW, Cha JK, et al. Primary mucosa-associated lymphoid tissue lymphoma metachronously involving esophagus and stomach. Korean J Gastroenterol **67**: 257-261, 2016.
24. Moriya K, Tamura H, Nakamura K, Hosone M, Inokuchi K. A primary esophageal MALT lymphoma patient with Helicobacter pylori infection achieved complete remission after H. pylori eradication without anti-lymphoma treatment. Leuk Res Rep **7**: 2-5, 2016.
25. Ma Q, Zhang C, Fang S, et al. Primary esophageal mucosa-associated lymphoid tissue lymphoma: a case report and review of literature. Medicine (Baltimore) **96**: e6478, 2017.
26. Liang R, Todd D, Chan TK, et al. Prognostic factors for primary gastrointestinal lymphoma. Hematol Oncol **13**: 153-163, 1995.
27. Pereira MI, Medeiros JA. Role of *Helicobacter pylori* in gastric mucosa-associated lymphoid tissue lymphomas. World J Gastroenterol **20**: 684-698, 2014.
28. Iwamuro M, Takenaka R, Nakagawa M, et al. Management of gastric mucosa-associated lymphoid tissue lymphoma in patients with extra copies of the MALT1 gene. World J Gastroenterol **23**: 6155-6163, 2017.
29. Tsai SJ, Lin CC, Chang CW, et al. Benign esophageal lesions: endoscopic and pathologic features. World J Gastroenterol **21**: 1091-1098, 2015.
30. Rohatiner A, d'Amore F, Coiffier B, et al. Report on a workshop convened to discuss the pathological and staging classifications of gastrointestinal tract lymphoma. Ann Oncol **5**: 397-400, 1994.