

## A Case of Primary Esophageal B-cell Lymphoma of MALT type, Presenting as a Submucosal Tumor

The primary esophageal lymphoma is extremely rare, and shows various morphologic characteristics. Only a single case of mucosa-associated lymphoid tissue (MALT) type lymphoma confined to the esophagus has been reported in the literature. A 61-yr-old man was referred to our hospital for evaluation of an esophageal submucosal tumor (SMT) that had been detected incidentally by endoscopy. He had a history of pulmonary tuberculosis with long-term anti-tuberculosis medication 15 yr before, and also had a history of syphilis, which had been treated one year before. He had been taking a synthetic thyroid hormones for the past 10 months because of an autoimmune thyroiditis. Endoscopy showed a longitudinal round and tubular shaped smooth elevated lesion, which was covered with intact mucosa and located at the mid to distal esophagus, 31 cm to 39 cm from the incisor teeth. Endoscopic ultrasonography (EUS) showed a huge longitudinal growing intermediate- to hypo-echoic mass located in the submucosal layer with internal small, various sized honeycomb-like anechoic lesions suggesting germinal centers. Subsequently, he underwent a surgery, which confirmed the mass as a primary esophageal low-grade B-cell lymphoma of MALT type.

Key Words : MALT; Lymphoma; Esophagus; Endosonography

Chan Sup Shim, Joon Seong Lee,  
Jin Oh Kim, Joo Young Cho,  
Moon Sung Lee, So Young Jin\*,  
Wook Youm<sup>†</sup>

Institute for Digestive Research, Department of Pathology\*, Department of Chest Surgery<sup>†</sup>, College of Medicine, Soon Chun Hyang University, Seoul, Korea

Received : 9 March 2002  
Accepted : 25 April 2002

### Address for correspondence

Chan-Sup Shim, M.D.  
Institute for Digestive Research, Digestive Disease Center College of Medicine, Soon Chun Hyang University, 657 Hannam-dong, Yongsan-gu, Seoul 140-743, Korea  
Tel : +82-2-709-9681, Fax : +82-2-749-1968  
E-mail : schidr@hosp.sch.ac.kr

## INTRODUCTION

The gastrointestinal tract is the most commonly involved extranodal site in non-Hodgkin's lymphoma (1, 2). However, the esophageal involvement by lymphoma is the rarest event, accounting for less than 1% of patients with lymphoma (1-3). Since Isaacson and Wright introduced the concept of mucosa-associated lymphoid tissue (MALT) lymphoma in 1984 (4), there have been many reports regarding primary gastrointestinal MALT lymphoma, especially primary gastric MALT lymphoma. To our knowledge, only one case of primary esophageal MALT lymphoma has been reported (5). Recent advancement in endoscopic ultrasonography (EUS) provides detailed structural abnormalities and depth of invasion in various gastrointestinal diseases including gastric lymphoma (6). Usually, gastric MALT lymphoma presents itself as a thickening of the mucosa and submucosa layer in the gastric wall, or discrete tumor masses; however, nearly all cases show infiltration of the mucosa (7, 8). We report a case of primary esophageal MALT lymphoma presenting itself as a large submucosal tumor (SMT), which was examined by endoscopic ultrasonography.

## CASE REPORT

A 61-yr-old man was referred to Soon Chun Hyang Uni-

versity hospital for evaluation of an esophageal SMT that had been detected incidentally by endoscopy. The patient denied dysphagia and any systemic symptoms. He had a history of pulmonary tuberculosis, which had been completely healed after a long-term medication (isoniazid, rifampin, ethambutol, and pyrazinamide for 9 months) 15 yr before. He also had a history of syphilis, which had been completely treated one year before. He had been taking a Comthyroid<sup>®</sup> (a combination of synthetic hormones; levothyroxine 0.05 mg and liothyronine 0.0125 mg) daily for the past 10 months because of an autoimmune thyroiditis. His blood sugar level was slightly high, but had been well controlled by diet control and exercise. He had a history of alcohol abuse for over 20 yr. He had a 20-pack-year smoking history. Physical examination revealed no abnormal finding except slightly pale conjunctivae. Laboratory data included white blood cell count 7,100/ $\mu$ L (normal range, 4,000-10,000/ $\mu$ L), hemoglobin value 10.3 g/dL (normal range, 13-17 g/dL), MCV 79.9 fL (normal range, 81-96 fL), and platelet count  $307 \times 10^3$ / $\mu$ L (normal range,  $130-450 \times 10^3$ / $\mu$ L). Fasting blood sugar level was 93 mg/dL (normal range, 70-110 mg/dL) with HbA<sub>1c</sub> of 7.0% (normal range, 3.8-5.4%). Thyroid function test revealed TSH 1.89  $\mu$ U/mL (normal range, 0.25-4.0  $\mu$ U/mL), T3 uptake 27.9% (normal range, 23-34%), T3 116.2 ng/dL (normal range, 60-190 ng/dL), and T4 7.73  $\mu$ g/dL (normal range, 4.5-11  $\mu$ g/dL). Both thyroglobulin antibodies and microsomal antibodies were positive (1.49 U/mL and 2.2 U/mL, respectively; normal range,



Fig. 1. Endoscopic view of the large longitudinal round mass with normal overlying mucosa in mid and distal esophagus.

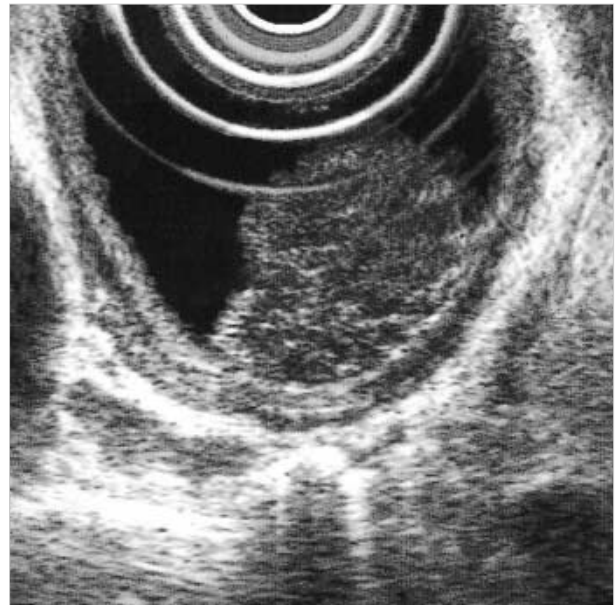


Fig. 2. Endoscopic ultrasonogram showing a well-demarcated,  $2 \times 1.5 \times 8$  cm-sized, lobulated mass with intermediate echoic pattern and honeycomb-like multiple small anechoic lesions, originating from the third hyperechoic layer (submucosa), consistent with a submucosal tumor such as esophageal stromal cell tumor or cavernous hemangioma.

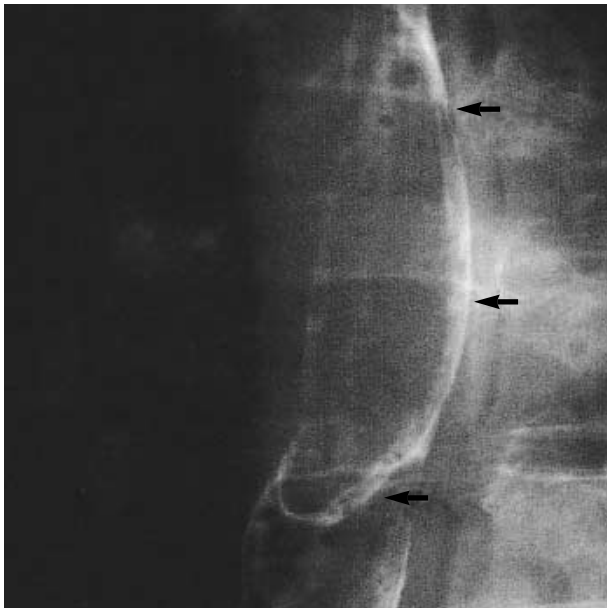


Fig. 3. Esophagogram showing a large submucosal tumor (arrows) with luminal narrowing, about 10 cm in length, in mid and distal esophagus.

$<0.3$  U/mL for both).

Initial endoscopy showed a longitudinal round and tubular shaped smooth elevated lesion, which was covered with intact normal mucosa and located at the mid to distal esophagus, 31 cm to 39 cm (2 cm from the Z-line) from the incisor teeth. There was no such finding as reflux esophagitis or Barrett's esophagus (Fig. 1). EUS showed an intermediate echoic mass, which was located in the deep mucosal and submucos-

al layer and measured  $2 \times 8$  cm. The mass was well demarcated, lobulated, and had multiple small anechoic lesions (honeycomb in appearance) within its solid portion (Fig. 2). A small round hypoechoic mass of 1.0 cm in diameter was also shown around the esophageal wall from the aorticopulmonary (AP) window, suggesting regional lymph node hyperplasia. These findings suggested the possibility of the esophageal stromal cell tumor or cavernous hemangioma. He was discharged without further evaluation including EUS-guided aspiration cytology for the proper tissue diagnosis.

There was no change in EUS findings 6 months after discharge. Barium esophagogram showed a smooth elongated protruded mass lesion in the distal esophagus, 2 cm above the esophagogastric junction, and this finding was compatible with a stromal tumor (Fig. 3). Dynamic chest computed tomography showed a well-defined, poorly enhanced mass in the distal esophagus, suggesting an esophageal SMT. Two small lymph nodes were also detected in the paraseptal region and AP window. There was a centrilobular and paraseptal emphysema. Abdominal ultrasonography showed normal abdominal organs, except for a mild fatty liver.

Surgical resection was performed under the impression of esophageal stromal cell tumor. After exposure of distal esophagus and confirmation of the exact tumor site, longitudinal myotomy was done along the tumor and we tried to separate the tumor mass from the mucosa. However, since the tumor was unusual for stromal cell tumor and had different pathologic characteristics, it was impossible to separate the tumor

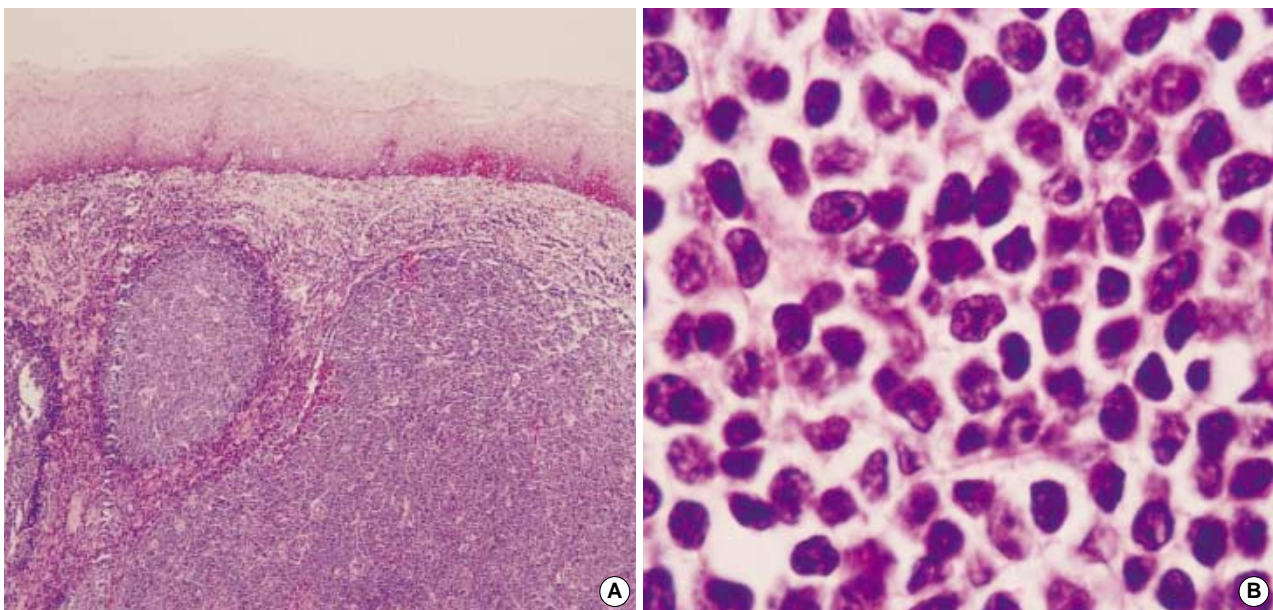


Fig. 4. (A) Histologic section disclosed proliferation of lymphoid cells in a large follicular pattern with occasional germinal center formation (H&E,  $\times 40$ ). (B) Proliferating lymphoid cells had central nuclei with irregular nuclear membrane and abundant clear cytoplasm (H&E,  $\times 1,000$ ).

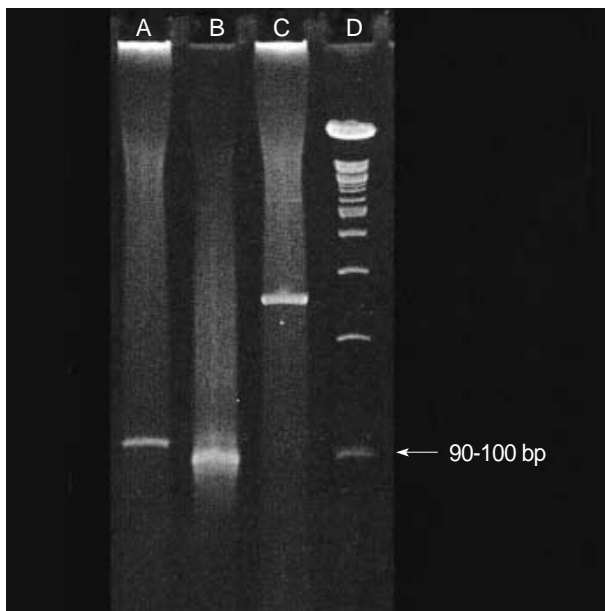


Fig. 5. Molecular analysis of immunoglobulin heavy chain gene rearrangement by polymerase chain reaction using FR3A-LJH as a primary PCR (Lane A) and using FR3A-VLJH as a secondary PCR (Lane B). A monoclonal dominant band corresponding to a monoallelic clonal rearrangement was noted on 90-100 bp (Lane B). Lane C, beta-globin control; Lane D, molecular markers.

mass from the mucosa. We removed the elongated tumor mass with underlying mucosa and closed the remaining mucosa and muscle separately layer by layer, and then covered the myo-

tomy site with a pleural flap. The gross examination of the surgical specimen revealed a well-circumscribed multinodular grayish white mass ( $6 \times 2 \times 1.5$  cm), which was covered by normal esophageal mucosa on one side. The cut surface was creamy yellow and lobulated in appearance. Histologically the esophageal mucosa was unremarkable. The lamina propria and the submucosa were replaced by dense infiltration of lymphoid cells. These lymphoid cells were arranged in large follicles with occasional germinal centers. Proliferating lymphoid cells were relatively monotonous centrocyte-like cells with irregular nuclear membrane and abundant clear cytoplasm (Fig. 4). Immunohistochemistry disclosed positive staining for CD20, Bcl 2, and CD10 and negative staining for Bcl 6, CD3, CD5, and cyclin D1. These cells showed a monoclonal restriction pattern for the kappa light chain on immunostaining and a positive monoclonal band for immunoglobulin heavy chain gene rearrangement (Fig. 5). These findings were consistent with a low-grade B-cell lymphoma of MALT type. Regional lymph nodes showed reactive hyperplasia.

Follow-up endoscopy with rapid urease test after surgery showed mild atrophic gastritis with *Helicobacter pylori* infection, so he received the modified triple therapy (clarithromycin, amoxicillin, and proton pump inhibitor for 1 week) and eradication of *H. pylori* was confirmed one month later.

## DISCUSSION

MALT lymphoma is a distinct subgroup of non-Hodgkin's lymphoma with particular clinicopathologic characteristics.

The gastrointestinal tract is the most commonly involved site, but it may be observed in the lungs, breast, bladder, conjunctiva, kidney, liver, skin, salivary glands, thyroid, and thymus (9).

Organized MALT within the gastrointestinal tract is distributed throughout the small intestine, appendix, and colon, forming Payer's patches, but is normally not found within the stomach mucosa, esophageal mucosa, salivary gland, or thyroid. However, MALT lymphoma usually develops from acquired MALT rather than the primary organized MALT. These acquired MALT tend to appear in patients with a history of autoimmune diseases or chronic inflammatory disorders. In the stomach, this lesion is induced by long-standing gastric infection with *H. pylori* and gastric MALT lymphoma may eventually develop as a result of persistent immunological stimulation. Acquired MALT also develops within the salivary glands, thyroid or lungs as a result of myoepithelial sialoadenoiditis, due to Sjogren's syndrome, Hashimoto thyroiditis, and interstitial lymphoid pneumonia (9, 10).

In our patient, the MALT lymphoma developed in the submucosal layer and was found only in the mucosa and submucosal layer of the esophagus definitely apart from the cardia although he had the *H. pylori* infection in his stomach. Atypical hyperplastic lymphoproliferative responses are known to occur due to Epstein-Barr virus, human immunodeficiency virus (HIV), human T-cell leukemia/lymphoma virus type I (HTLV-I), and certain drugs, and in post-transplant organ recipients, in autoimmune disorders, and in acquired or genetic hypogammaglobulinemias (11). In our patient, we could not detect the exact cause of esophageal MALT lymphoma, however, there were potential risk factors, such as an autoimmune disorder, drugs, and chronic periesophageal inflammation, which were supported by the presence of autoimmune thyroiditis, history of long-term anti-tuberculosis medication, and treatment of syphilis, respectively.

Usually CD10 expression has been described as the sensitive and specific marker of follicular center cell lymphoma. Recently the specificity of CD10 expression was challenged due to observation of CD10 expression in the neoplastic T cells of angioimmunoblastic T-cell lymphoma (12). Therefore CD10/Bcl-6 coexpression is regarded as a reliable marker for follicular center B cell differentiation (13). Though CD10 was positive in our patient, the possibility of malignant lymphoma of follicular center cell origin is less likely because CD 10 expression is not accompanied by Bcl-6.

The major finding of low-grade gastric MALT lymphoma on EUS, as has been suggested in many reports, is the thickening of the wall layer, especially the first to the third layer (8, 9, 14, 15). Some cases show discrete tumor masses destroying the mucosal layer. However, our case presented itself as a well-demarcated SMT-like intermediate- to hypo-echoic mass located in the submucosal layer, which misled us to an impression of esophageal stromal cell tumor or cavernous hemangioma. Internal, small, various sized, honeycomb-like anechoic lesions may suggest germinal centers. In general, the lymphomatous involvement of the gastric wall proceeds mainly

by longitudinal (or horizontal) growth within the wall, while the growth of cancer is predominantly vertical with early invasion of the deep wall. Mucosal involvement in lymphoma is often less extensive than the infiltration of underlying layers (16). From these observations, we considered the EUS findings of our case to suggest a low-grade lymphoma, because the lymphoma of the patient had developed in the submucosal layer and was found only in the mucosa and submucosal layer of the esophagus, representing a longitudinal SMT.

Another case of primary esophageal MALT lymphoma reported also presented itself as a SMT-like lesion, which was very similar to our case, despite the lack of description of pathologic findings (5). To our knowledge, these two cases are the only reported cases of primary esophageal MALT lymphoma, which showed a predominant esophageal involvement without peripheral or mediastinal lymph node involvement, as well as splenic or hepatic involvement, and a normal white cell count (17). This SMT-like growth might be a characteristic of primary esophageal MALT lymphoma.

## REFERENCES

1. Amer MH, El-Akkad S. *Gastrointestinal lymphoma in adults: clinical features and management of 300 cases. Gastroenterology* 1994; 106: 846-58.
2. Herrmann R, Panahon A, Barcos MP, Walsh D, Stutzman L. *Gastrointestinal involvement in non-Hodgkin's lymphoma. Cancer* 1980; 46: 215-22.
3. Taal BG, Van Heerde P, Somers R. *Isolated primary oesophageal involvement by lymphoma: a rare cause of dysphagia: two case histories and a review of other published data. Gut* 1993; 34: 994-8.
4. Isaacson P, Wright DH. *Extranodal malignant lymphoma arising from mucosa-associated lymphoid tissue. Cancer* 1984; 53: 2515-24.
5. Nishiyama Y, Yamamoto Y, Ono Y, Satoh K, Ohkawa M, Yamauchi A, Tanabe M. *Visualization of esophageal non-Hodgkin's lymphoma with Ga-67 scintigraphy. Ann Nucl Med* 1999; 13: 419-21.
6. Shim CS. *Role of endoscopic ultrasonography for gastric lesions. Endoscopy* 1998; 30 (Suppl 1): A55-9.
7. Pavlick AC, Gerdes H, Portlock CS. *Endoscopic ultrasound in the evaluation of gastric small lymphocytic mucosa-associated lymphoid tumors. J Clin Oncol* 1997; 15: 1761-6.
8. Sackmann M, Morgner A, Rudolph B, Neubauer A, Thiede C, Schulz H, Kraemer W, Boersch G, Rohde P, Seifert E, Stolte M, Bayerdoerfer E, MALT Lymphoma study group. *Regression of gastric MALT lymphoma after eradication of Helicobacter pylori is predicted by endosonographic staging. Gastroenterology* 1997; 113: 1087-90.
9. Thieblemont C, Berger F, Coiffier B. *Mucosa-associated lymphoid tissue lymphomas. Curr Opin Oncol* 1995; 7: 415-20.
10. Weston AP, Cherian R, Horvat RT, Lawrinenko V, Dixon A, McGregor D. *Mucosa-associated lymphoid tissue (MALT) in Barrett's esophagus: prospective evaluation and association with gastric MALT, MALT lymphoma, and Helicobacter pylori. Am J Gastroenterol* 1997;

- 92: 800-4.
11. Harrington DS, Masih AS, Purtilo DT. *Atypical immune proliferations*. In: Hoffman R, Benz EJ, Shattil SJ, Furie B, Cohen HJ, Silberstein LE, editors. *Hematology. Basic principles and practice*. 2nd ed. New York: Churchill-Livingstone; 1995: 1387-99.
  12. Attygalle A, Al-Jehani R, Diss TC, Munson P, Liu H, Du MQ, Issacson PG, Dogan A. *Neoplastic T cells in angioimmunoblastic T-cell lymphoma express CD10*. *Blood* 2002; 99: 627-33.
  13. Ree HJ, Yang WI, Kim CW, Huh J, Lee SS, Cho EY, Ko YH, Chamey D. *Coexpression of Bcl-6 and CD10 in diffuse large B-cell lymphomas: significance of Bcl-6 expression patterns in identifying germinal center B-cell lymphoma*. *Hum Pathol* 2001; 32: 954-62.
  14. Nobre-Leitao C, Lage P, Cravo M, Cabeçadas J, Chaves P, Alberto-Santos A, Correia J, Soares J, Costa-Mira F. *Treatment of gastric MALT lymphoma by Helicobacter pylori eradication: a study controlled by endoscopic ultrasonography*. *Am J Gastroenterol* 1998; 93: 732-6.
  15. Cheng PN, Sheu BS. *Application of endoscopic sonography to monitor the resolution of H. pylori-related gastric MALToma*. *Endoscopy* 2000; 32: A45 (P119).
  16. Caletti G, Bocus P, Togliani T, Roda E. *Gastric lymphoma, infiltrative disorders, and large gastric folds*. In: van Dam J, Sivak MV editors. *Gastrointestinal Endoscopy*. 1st ed. Philadelphia; WB Saunders Co; 1999: 175-83.
  17. Dawson IMP, Cornes JS, Morson BC. *Primary malignant lymphoid tumours of the intestinal tract*. *Br J Surg* 1961; 49: 31-84.