CASE REPORT

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

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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

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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...
surgical resection of colon cancer, and it was curatively re-
sected. She had been treated for Hashimoto’s thyroiditis
since 70 years of age. The patient had no history of esopha-
geal or gastroduodenal disease. A physical examination re-
vealed no abnormalities, and there were no lymphadenopa-
thies. 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 Helicobac-
ter 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, 1B). On 18F-fluorodeoxyglucose posi-
tron emission tomography, the tracer uptake was noted only
in the esophagus (Fig. 1C). There were no lymphadenopa-
thies on computed tomography. Esophagogastroduodenosco-
py revealed a solitary subepithelial tumor, approximately
20 mm in diameter (Fig. 2A: white light image, 2B: narrow
band imaging, 2C: post-indigo carmine spraying). Endo-
scopic ultrasonography showed a homogenous, hypoechoic
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). Immunohistochemical studies revealed that the lymphoid cells were positive for CD20, weakly positive for BCL2, and negative for CD3, CD10, and cyclin D1. The percentage of tumor cells positive for Ki-67 staining was less than 1%, indicating few mitotic cells. The diagnosis of esophageal MALT lymphoma was confirmed based on these
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

**Discussion**

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

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

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


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.
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 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

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