CASE REPORT

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PRIMARY MUCOSA-ASSOCIATED LYMPHOID TISSUE (MALT) LYMPHOMA OF THE LARYNX

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Abstract: Background. Mucosa-associated lymphoid tissue (MALT) lymphoma is usually associated with a chronic inflammatory disease from which lymphoid tissue of MALT type arises as a prerequisite for lymphoma proliferation. No well-characterized chronic inflammatory process has been identified in the larynx.

Methods. We report a case of primary MALT lymphoma of the larynx associated with extraesophageal reflux, chronic laryngitis, and gastric Helicobacter pylori infection, raising the issue of its physiopathology and treatment.

Results. Treatment of this MALT lymphoma of the larynx consisted of complete surgical excision associated with omeprazole, amoxicillin, and clarithromycin. No evidence of disease was observed after 24 months of follow-up.

Conclusions. We may assume that chronic laryngitis could be a precursor to MALT lymphoma. This case is the first one to our knowledge of a primary MALT lymphoma of the larynx treated with conservative management combining surgical excision, reflux therapy, and eradication of gastric H. pylori infection. © 2005 Wiley Periodicals, Inc. Head Neck 27: 258–262, 2005

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Primary lymphoma of the larynx is rare. Lymphoma of the mucosa-associated lymphoid tissue (MALT) type is a distinct clinicopathologic entity belonging to the subset of marginal zone B-cell lymphomas. MALT lymphoma was first described in 1983 in the gastrointestinal tract.1 The laryngeal location was reported later by Diebold et al in 1990.2 Primary MALT lymphoma of the larynx represents a very rare entity. No more than 12 cases have been reported in the literature.

Being the most common and best studied, the gastric location has become the paradigm for the entire group of MALT lymphomas. There is often a history of chronic inflammatory diseases from which the lymphoma arises. Despite the association of gastric MALT lymphoma with chronic Helicobacter pylori infection,3 no well-characterized chronic inflammatory process has been clearly identified in the larynx until now.4 Also, despite the effective eradication of H. pylori with antibiotics in the treatment of gastric MALT lymphoma, no specific treatment has been identified for MALT lymphoma of nongastric locations.
We report a case of MALT lymphoma of the larynx associated with extraesophageal reflux, chronic laryngitis, and gastric *H. pylori* infection, raising the issue of both the physiopathology and the treatment of MALT lymphoma of the larynx.

**CASE REPORT**

A 46-year-old white man with a 6-month history of dysphonia was referred to our department. The medical history was unremarkable. He had no smoking history. The physical examination revealed a submucosal mass of the left false vocal fold. The overlying mucosa was normal in appearance. The vocal folds and arytenoid cartilages were symmetrically mobile. Signs of extraesophageal reflux were noted: posterior laryngitis and hypertrophy of the mucosa of the posterior commissure. There were no palpable cervical lymph nodes. The rhinopharynx and Waldeyer’s ring were clinically normal. The rest of the head and neck examination was within normal limits.

A CT scan demonstrated a well-circumscribed contrast-enhancing solid mass of the left paraglottic space (Figure 1). The mass measured 10 × 15 mm and did not extend into the pre-epiglottic space or into the subglottic region. The thyroid cartilage was normal. No lymph nodes were noted. The diagnosis of a tumor of the left paraglottic space was suggested. The patient was counseled regarding the variety of all possible histologic diagnoses. He gave informed consent for diagnosis and possible treatment by endoscopic CO₂ laser resection.

The patient first underwent a direct laryngoscopy under general anesthesia. A preliminary examination using a 0° optical instrument confirmed the presence of a submucosal tumor located into the left false vocal fold. The glottis, subglottis, epilarynx, and hypopharynx were normal. A double-balloon Laserflex endotracheal tube (Nellcor, Pleasanton, CA) was then placed for suspension microlaryngoscopy. The left false vocal fold was first incised along its axis. The mass was well circumscribed, whitish, and firm. The surgical excision of the mass was performed with a CO₂ laser (Acuspot; Sharplan, Tel Aviv, Israel) at a discontinuous pulse (every 0.1 second) at 3 watts. The tumor measured 1.5 × 1 cm. Resection was macroscopically complete. The postoperative course was unremarkable.

Pathologic examination demonstrated a diffuse and nodular infiltrate under a normal transitional epithelium. The diffuse infiltrate showed some germinal centers. The nodular infiltrate was composed of a mixture of small lymphoid cells, such as centrocyte-like lymphocytes, plasma cells, lymphoplasmacytoid cells, and monocytoid B cells (Figure 2). Immunohistochemical staining demonstrated that these centrocyte-like lymphocytes were mainly B cells (CD20+, CD79a+, CD5−, CD10−). In some glands, nests of tumor lymphoid cells were identified between the epithelial cells, corresponding to “lymphoepithelial lesions.” The margins of resection were free of tumor. The diagnosis of a MALT-type lymphoma of low-grade malignancy was based on the combination of centrocyte-like lymphocytes (B cells) with lymphoepithelial lesions and normal germinal centers.

The epithelium showed a nonspecific inflammation. Signs of *H. pylori* infection were searched for by histologic examination and immunohistochemical analysis (B471; DAKO, Glostrup, Denmark). No evidence of *H. pylori* was detected.

A postoperative workup was aimed at detection of extralaryngeal locations of the lymphoma. No
enlarged lymph nodes, liver, or spleen were palpable. Red and white blood count, sedimentation rate, renal and liver function tests, β2 microglobulin, and lactic dehydrogenase were normal. Hepatitis C virus serologic testing was negative. Bone marrow aspirate and biopsy specimens were normal. No pathologic lymph nodes or abnormalities of the liver and spleen were detected on thoracic and abdominal CT scans. Esogastroduodenal endoscopy demonstrated an antral gastritis. Biopsy specimens of the gastric mucosa showed an interstitial gastritis within the antrum. No MALT lymphoma lesions were seen. The presence of *H. pylori* was demonstrated on the biopsy specimens of the antrum. Total coloscopy with systematic biopsies found no evidence of lymphomatous lesions. The patient exhibited an excellent performance status and no B symptoms. This tumor was finally considered as resected stage 1A MALT lymphoma, according to the Ann Arbor Classification.5

Treatment of this primary and solitary MALT lymphoma of the larynx consisted of complete surgical excision associated with omeprazole, 20 mg twice per day, coupled with amoxicillin (500 mg four times per day) and clarithromycin (500 mg twice per day) for 10 days. Omeprazole was continued for 6 months, following guidelines from the committee on speech, voice, and swallowing disorders of the American Academy of Otolaryngology–Head and Neck Surgery.6

No evidence of disease was observed after 24 months of follow-up. The laryngeal examination was normal. Esogastroduodenal endoscopy with multiple biopsies demonstrated the eradication of the *H. pylori* and no evidence of gastritis.

**DISCUSSION**

MALT lymphoma is a distinct clinical and pathologic entity. It belongs to the category of the extranodal marginal zone B-cell lymphomas, according to the classification of the International Lymphoma Study Group7 and the World Health Organization.8 Clinically, MALT lymphomas commonly arise in the stomach. Other sites, including the lung, the digestive or urinary tract, the salivary glands, the thyroid, and the orbit, have been reported.9 MALT lymphomas rarely occur in the larynx. To date, only 11 cases have been reported in the literature. This could be explained by two facts. First, lymphomas in the larynx represent less than 1% of primary malignant tumors. Second, because the first description of MALT lymphoma of the larynx was made in 1990, some MALT lymphomas may have been misdiagnosed and eventually reported in the literature as a different type of lymphoma. Table 1 summarizes the reported cases of identified MALT lymphomas of the larynx.

Histologically, the normal stroma is replaced by a sheetlike nodular arrangement of atypical lymphoid cells mixed with germinal centers. The tumor proliferation contains centrocyte-like cells (typically CD20+, CD79a+, CD5−, and CD10−), plasma cells, monocyte-like cells, and lympho-plasmacyte-like lymphocytes in variable proportions. The characteristic lymphoepithelial lesion is composed of destructive infiltrates of individual glands by neoplastic centrocyte-like cells. Studies showed that these centrocyte-like cells have a monoclonal origin and characteristic genetic abnormalities.10,11

The physiopathology of MALT lymphoma is specific. Surprisingly, primary MALT lymphoma most commonly arises in organs normally devoid of MALT.12 There is often a chronic inflammatory disease during the course of which the organ acquires lymphoid tissue of MALT type.13 Gastric MALT lymphoma is associated with chronic *H. pylori* infection. Hashimoto’s thyroiditis is considered to be a risk factor for thyroid MALT lymphoma.14 Sjögren syndrome for salivary gland MALT lymphoma is known as a predisposing factor.15 Follicular bronchiectasis in the lung and inflammatory lesions of the orbit are thought to be other pre-existing disorders.16 The hepatitis C virus, which has been linked to B-cell lymphoproliferation and autoimmunity, has also been

<table>
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<tr>
<th>First author, year</th>
<th>No. lymphomas</th>
<th>Treatment</th>
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<tr>
<td>Deibold, 19902</td>
<td>1</td>
<td>Chemotherapy + radiotherapy (40 Gy)</td>
</tr>
<tr>
<td>Hisashi, 199425</td>
<td>1</td>
<td>Radiotherapy (30 Gy)</td>
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<tr>
<td>Horny, 199612</td>
<td>1</td>
<td>?</td>
</tr>
<tr>
<td>Kato, 199726</td>
<td>1</td>
<td>Chemotherapy + radiotherapy (50 Gy)</td>
</tr>
<tr>
<td>De Bree, 199827</td>
<td>1</td>
<td>Radiotherapy (28 Gy)</td>
</tr>
<tr>
<td>Zinzani, 19999</td>
<td>1</td>
<td>Radiotherapy</td>
</tr>
<tr>
<td>Cheng, 199921</td>
<td>1</td>
<td>Radiotherapy (30 Gy)</td>
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<tr>
<td>Gabrys, 199928</td>
<td>1</td>
<td>Chemotherapy</td>
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<tr>
<td>Tsang, 200118</td>
<td>1</td>
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<tr>
<td>Usui, 200029</td>
<td>1</td>
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</tr>
<tr>
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<td>Debaja, 200330</td>
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Abbreviation: MALT, mucosa-associated lymphoid tissue.

# Table 1. MALT lymphomas of the larynx reported in the literature.
localized in several tissues, including gastric mucosa. All these chronic inflammatory diseases are thought to induce the formation of the lymphoid tissue in the organ that is devoid of native MALT as a prerequisite for MALT lymphoma proliferation.

The adult larynx usually has no MALT. No well-characterized chronic inflammatory process in the larynx has been found to be a precursor to MALT lymphoma. In this case, H. pylori could not be retained as precursor, because it was not found in the larynx. Hepatitis C was absent. A patent chronic laryngitis caused by extraesophageal reflux was present, however. This was the only chronic inflammatory process found. We may assume that chronic laryngitis could be a precursor to MALT lymphoma. Extraesophageal or laryngopharyngeal reflux is a well-known cause of chronic laryngitis. Chronic laryngitis may induce and develop the formation of lymphoid tissue in the larynx. Further clinical, pathologic, and immunologic studies about reflux and submucosal lymphoid tissue infiltration are indicated.

The optimal treatment approach for extranodal marginal zone B-cell lymphomas of MALT type is evolving. Being the most common and best-studied MALT lymphoma, the gastric location has become the paradigm for the entire group of MALT lymphomas. Increasing evidence indicates that eradication of H. pylori with antibiotics can be effectively used as the sole initial treatment. This led to the concept that MALT lymphoma can be cured with the eradication of the underlying antigenic stimulus. Unfortunately, no specific treatment has been identified to date for nongastric locations. The treatment has to be tailored to the specific site. Although radiation therapy and chemotherapy are the most common treatments advocated worldwide, local intralesional administration of alpha-2a interferon was successfully performed for conjunctival and lacrimal gland sites in five patients. Most MALT lymphomas of the larynx have been treated with radiation therapy when the disease was localized and with chemotherapy in cases of recurrent or disseminated disease (Table 1). Local radiation therapy has been advocated as the most appropriate treatment, in that other lymphomas are highly sensitive to this treatment. Radiation therapy is generally moderate-dose radiotherapy (30–50 Gy). Surprisingly, surgical excision has not been reported, although early clinical stages may be curable by local resection.

The case reported here is the first one to our knowledge of a primary MALT lymphoma of the larynx treated with a conservative management combining surgical excision, reflux therapy, and eradication of gastric H. pylori infection. In our opinion, in the treatment process, the chronic inflammatory disorder should be treated. Therefore, reflux therapy may be a distinct adjunct to treat the chronic inflammatory disease of the larynx and may even be of primary importance in the treatment of primary laryngeal MALT lymphoma. In our view, conservative treatment should be advocated for primary MALT lymphoma of the larynx if complete surgical excision is feasible. MALT lymphomas are low-grade malignancies. They tend to remain localized for a long time and rarely disseminate. In the few series published of nongastrointestinal MALT lymphomas, patients seem to have an excellent outcome, with a 5-year overall survival ranging from 86% to 100% despite the fact that 25% had a disseminated disease. Considering this general prognosis, conservative management may prevail over systemic treatments and radiation therapy because of potential complications. Recurrence may happen. No treatment guidelines exist for the management of patients after local recurrence. Low-grade MALT lymphomas can transform to high-grade lymphomas. Systemic chemotherapy and radiation therapy can be used in such cases. According to preliminary data, anti-CD20 antibodies may also have significant clinical activity.

We recommend a strict laryngeal and gastric endoscopic follow-up with multiple biopsies to monitor the disappearance of the lymphoma and the persistent eradication of H. pylori.

In conclusion, because of the scarcity of cases reported, the physiopathology and treatment of primary MALT lymphoma of the larynx is still poorly understood. Part of our treatment regimen was based on the assumption that extraesophageal reflux causing chronic laryngitis may be involved in the physiopathology of the disease. Further studies of chronic laryngitis may help to understand the mechanisms involved and the optimal treatment for primary MALT lymphoma of the larynx.

REFERENCES


