

Case Report

# Subglottic stenosis induced by extranodal mucosa-associated lymphoid tissue lymphoma

Ji-Rung Kuo<sup>a</sup>, Yu-Yi Hou<sup>a,c,\*</sup>, Sau-Tung Chu<sup>a</sup>, Chu-Chun Chien<sup>b</sup>

<sup>a</sup>Department of Otolaryngology, Kaohsiung Veterans General Hospital, Kaohsiung, Taiwan, ROC

<sup>b</sup>Department of Pathology, Kaohsiung Veterans General Hospital, Kaohsiung, Taiwan, ROC

<sup>c</sup>Yuh-Ing Junior College of Health Care & Management, Kaohsiung, Taiwan, ROC

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## Abstract

Mucosa-associated lymphoid tissue (MALT) lymphoma is usually associated with a chronic inflammatory disease or autoimmune disorders from which lymphoid tissue of MALT type arises as a prerequisite for lymphoma proliferation. Primary hematopoietic neoplasms of the larynx are rare. MALT lymphomas of the larynx are believed to arise from preexisting or acquired lymphoid tissue of the upper airway which is documented in the supraglottic region. Therefore, these are mainly located in the supraglottic and glottic areas, with only a few reported in the subglottic region. We report on a 50-year-old woman with a hoarseness, stridor, and developing exertional dyspnea. On indirect laryngoscope, multiple nodular lesions with smooth surface over the subglottis with subglottic stenosis was found. The biopsy confirmed the diagnosis of a MALT lymphoma. We hope to promote awareness and consideration of MALT lymphoma in the differential diagnosis in subglottic stenosis. Copyright © 2011 Elsevier Taiwan LLC and the Chinese Medical Association. All rights reserved.

**Keywords:** Larynx; MALT lymphoma; Subglottic stenosis

## 1. Introduction

Primary lymphoma of the larynx is rare. MALT lymphoma was first described by Isaacson and Wright in 1983 to characterize the histologic features of low-grade B-cell lymphoma of extranodal origin such as the stomach, salivary gland, or thyroid gland.<sup>1</sup> The laryngeal location was reported later by Diebold in 1990. 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* (*H. pylori*) infection, no well characterized chronic inflammatory process has been clearly identified in the larynx until now.<sup>2</sup> The larynx may contain diffuse and follicular lymphoid tissue which is located mainly in the supraglottis. Most cases of primary laryngeal MALT lymphoma are

believed to arise from preexisting or acquired lymphoid tissue in the supraglottic region.<sup>3</sup> In this article, we report a very rare case of subglottic stenosis induced by MALT lymphoma.

## 2. Case report

A 50-year-old woman had a 3-month history of hoarseness, stridor and developing exertional dyspnea. Her medical history was unremarkable, and she had no history of autoimmune disorders. The physical examination revealed swelling over bilateral subglottic areas. The rest of the head and neck examination was within normal limits. Chest X-ray demonstrated no active lung lesions or nodular lesions. Indirect fibroscopy revealed multiple nodular lesions with smooth surface over the subglottic region with subglottic stenosis (Fig. 1). A computed tomography (CT) scan demonstrated increased soft tissue over the subglottic mucosa with airway narrowing (Fig. 2). Circumferential tracheal wall thickening of vocal cord and subglottic region were noted, with length of about 3 cm. The patient underwent a direct laryngoscopy under general

\* Corresponding author. Dr. Yu-Yi Hou, Department of Otolaryngology, Kaohsiung Veterans General Hospital, 386, Ta-Chung 1<sup>st</sup> Road, Kaohsiung 813, Taiwan, ROC.

E-mail addresses: [piraty@hotmail.com](mailto:piraty@hotmail.com), [yyhou@vghks.gov.tw](mailto:yyhou@vghks.gov.tw) (Y.-Y. Hou).

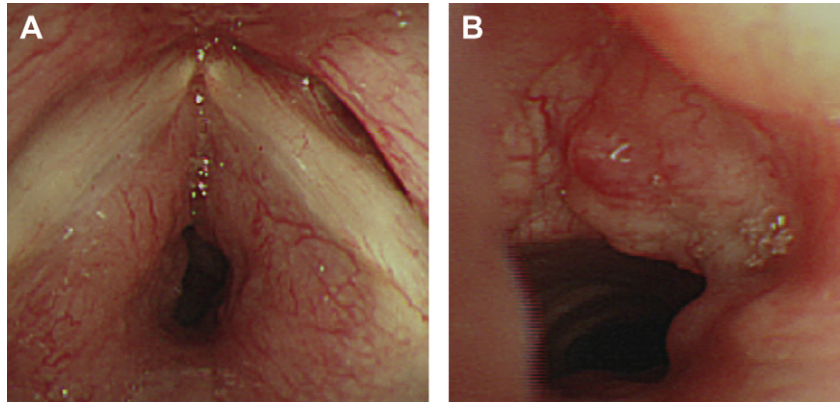


Fig. 1. Multiple nodular lesions with smooth surface over subglottic region with subglottic stenosis seen on indirect fibroscope. (A) Level of the glottic area. (B) Level of subglottic area.

anesthesia for confirming the presence of multiple nodular lesions with smooth surface over the subglottic region. The surgical excision for visible nodular lesions was performed. The biggest tumor measured  $0.3 \times 0.3 \times 0.3 \text{ cm}^3$  and was sent for permanent pathology.

Histopathologic examination including immunohistochemistry was performed, and the specimens contained a monotonous proliferation of small to medium-sized lymphoid cells resembling small centrocytes, monocytoid B cells, small lymphoid cells, and plasma cells (Fig. 3A). Infiltration of the surface epithelium by lymphoid cells resulted in characteristic lymphoepithelial lesions. The tumor cells demonstrated strong coexpression of CD20 (Fig. 3B) and BCL2 (Fig. 3C). Staining for CD3, CD5, CD10, CD23, and cyclin D1 was consistently negative. The diagnosis of a MALT lymphoma was based on the combination of centrocyte-like lymphocytes (B cells) with lymphoepithelial lesions and normal germinal centers.

A postoperative work-up was aimed at detection of extralaryngeal locations of the lymphoma or underlying autoimmune disorders. Red and white blood counts, sedimentation rate, renal, liver, thyroid function tests, rheumatoid factor, anti-nuclear antibodies, anti-RO antibodies, anti-LA antibodies and

thyroid antibodies were normal. Bone marrow aspirate and biopsy specimens were normal. No pathologic lymph nodes were detected on CT scans. Esogastroduodenal endoscopy demonstrated mild sliding hiatal hernia.  $^{13}\text{C}$ -urea breath test ( $^{13}\text{C}$ -UBT) was performed and the excretion value is 10.2 per mil (normal range  $<2.0$  per mil). Positron emission tomography demonstrated glucose hypermetabolism in the posterior wall of the subglottic region. The tumor was finally considered as subglottis low-grade MALT-type B-cell non-Hodgkin's lymphoma complicated with subglottic stenosis.

The patient was referred to the Department of Hematology and Oncology for continued management. Treatment of this case consisted of complete surgical excision associated with pantoprazole, 40 mg twice per day, coupled with amoxicillin (1,000 mg twice per day) and clarithromycin (500 mg twice per day) for 7 days. Then,  $^{13}\text{C}$ -UBT was rechecked one month later and the excretion value was 14.0 per mil. Fibroscopy was performed again, and swelling over subglottic area was seen. CT was rechecked and demonstrated persistent increased soft tissue in the subglottic mucosa region. Therefore, further radiotherapy or chemotherapy was suggested. Unfortunately, patient and her family hesitated about it and later refused.

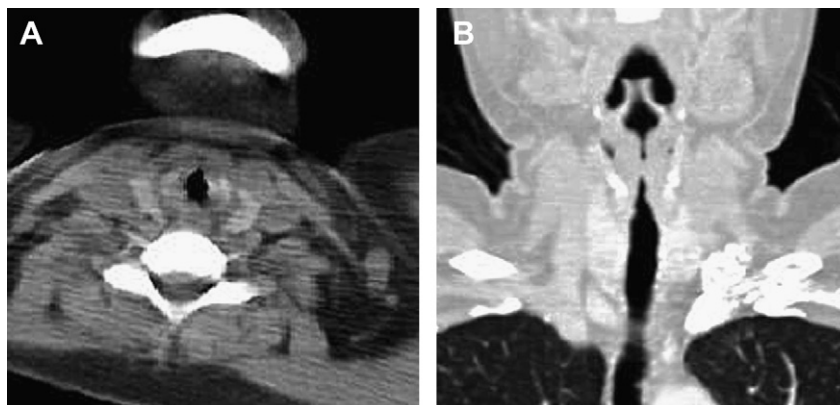


Fig. 2. Computed tomography scan of larynx showing soft tissue over subglottic mucosa with airway narrowing and circumferential tracheal wall thickening of vocal cord and subglottic region with length about 3 cm. (A) Axial view. (B) Coronal view.

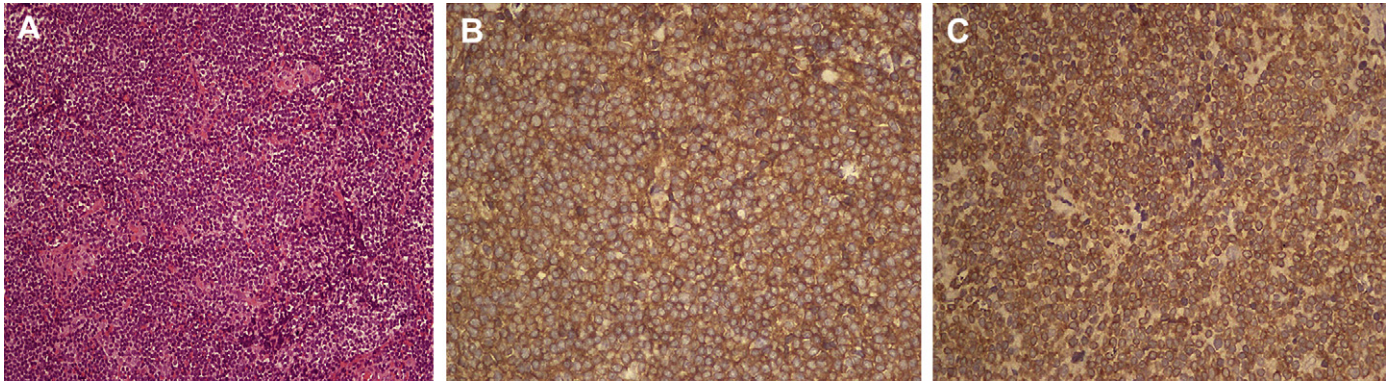


Fig. 3. Histologic and immunophenotypic features of biopsy specimen. (A) Hematoxylin and eosin stain displays dense lymphoid infiltrates (original, 200 $\times$ ). There is expression of (B) CD20 (original, 400 $\times$ ) and (C) BCL2 (original, 400 $\times$ ).

### 3. Discussion

MALT lymphoma belongs to the category of the extranodal marginal zone B-cell lymphomas. Gastric lymphoma is so far the most common type of the MALT lymphomas, comprising about 80% of all MALT lymphomas. They have also been reported in the thyroid gland, salivary gland, conjunctiva, thymus, breast, lung, kidneys, and urinary bladder. Extra-gastric MALT lymphoma are thought to arise predominantly in about 39% of patients with autoimmune diseases,<sup>4</sup> such as rheumatoid arthritis, systemic lupus erythematosus, Sjogren's syndrome, and Hashimoto's thyroiditis.<sup>5</sup>

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 lymphoplasmacyte-like lymphocytes in variable proportions.<sup>6</sup> Gastric MALT lymphoma is associated with chronic *H pylori* infection. Besides *H pylori*, bacteria such as *Campylobacter jejuni*, *Borellia burgdorferi*, or *Chlamydia psittaci*<sup>7</sup> have also been implicated in the development of MALT lymphoma.<sup>13</sup> C-urea breath test is non-invasive diagnosis of *H pylori* infection with a sensitivity and specificity greater than 90%.<sup>8</sup> But there are other urease activity-possessing agents colonizing in the laryngeal tissue (*Campylobacter sp.*, *Corynebacterium sp.*, *Haemophilus sp.*, *Streptococcus salivarius*, *Candida sp.*, *Klebsiella pneumonia*, and *Proteus*). Thus, urease positivity is not specific enough to prove the presence of *H pylori* in laryngeal tissue. Thus, the most proper way to show the *H pylori* presence is culturing and polymerase chain reaction (PCR).<sup>9</sup> Real-time PCR assay showed sensitivity of 93.33% (negative predictive value, 90.90%) and specificity of 85.95% (positive predictive value, 90.32%).<sup>10</sup> The presence of the genomic material of *H pylori* within the laryngeal tissue of patients with squamous cell carcinoma of the larynx is a proof of the colonization of the bacterium in that tissue,<sup>11</sup> and biopsy of larynx for real-time PCR may be performed to exclude the possibility of *H pylori* infection. The larynx may contain diffuse and follicular lymphoid tissue and is documented in the

supraglottic region, and most cases are found over the supraglottis.<sup>3</sup> The detection of MALT lymphoma in larynx is very rare; less than 15 cases have been reported since its first description by Diebold, and only 3 cases over subglottis causing subglottic tracheal stenosis have been reported.<sup>12</sup>

The optimal treatment approach for MALT lymphoma is evolving. Increasing evidence indicates that eradication of *H pylori* with antibiotics can be effectively used as the sole initial treatment.<sup>13</sup> Unfortunately, no specific treatment has been identified for nongastric location. The treatment consists of radiotherapy if the disease is localized or chemotherapy if disseminated, and the possibility of using new therapeutic approaches, including immunotherapy, proteasome inhibitors, and oxaliplatin.<sup>14</sup> Local radiation therapy has been advocated as the most appropriate treatment in this area due to highly sensitivity to MALT lymphoma over larynx.<sup>15</sup> In general, patients with MALT lymphoma respond well to local therapy and have high survival rate.<sup>6</sup> The 5-year survival rate is about 80%.<sup>16</sup>

In conclusion, the physiopathology and treatment of primary MALT lymphoma of the larynx is still poorly understood. The interest of this case lies in the rare involvement of hematopoietic neoplasms in the larynx, especially in the subglottis and causing a subglottic stenosis. We hope to promote awareness and consideration of MALT lymphoma in the differentiated diagnosis in subglottic stenosis.

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