

## Subglottic MALT Lymphoma of the Larynx – More Attention to the Glottis

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**Abstract.** *Background: Mucosa-associated lymphoid tissue (MALT) lymphoma of the larynx is a rare but well-documented entity which may arise from chronic inflammatory process. Supraglottic left regions are predominant due to unknown reason. Case Report: We present the case of a 62-year-old man with a dry cough, stridor and developing exertional dyspnea. This subglottic almost circumferential MALT lymphoma showed a temporary distinct disappearance after cortisone administration during the diagnostic process. Bronchoscopy confirmed the diagnosis of a primary MALT lymphoma of the larynx. The patient received chemotherapy according to CHOP scheme plus rituximab. A reliable post-treatment care period of 15 months showed no sign of recurrence. Conclusion: MALT lymphoma of the larynx are believed to arise from preexisting or acquired lymphoid tissue of the upper airway. Acquired lymphoid tissue is documented in the supraglottic region and may be associated with a chronic inflammatory process. However, in subglottic cases it is unclear whether the chronic inflammation arises from a local or systemic process.*

Since the first description of lymphoma arising from mucosa-associated lymphoid tissue (MALT) as an entity by Isaacson and Wright in 1983 (1), several cases of laryngeal MALT were reported in a more or less anecdotal form, starting with Diebold and colleagues in 1990 (2). The case reported by Kobayashi *et al.* in 1992 is regarded as the first subglottic lymphoproliferative lesion in reported English literature with features of MALT lymphoma (3). We report a case of a

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subglottic MALT lymphoma which was evident during flexible bronchoscopy but waned almost entirely in a CT-scan of the neck region after a bolus administration of cortisone.

### Case Report

A 62-year-old male with adipositas was admitted and complained of a dry cough, increasing exertional dyspnea, and stridor for one year. Blood work and clinical examination were uneventful. In order to prevent edema due to mechanical manipulation, 250 mg cortisone were administered intravenously one hour prior to flexible bronchoscopy. The bronchoscopy revealed a circumferential subglottic lesion (Figure 1) and no tracheal or pulmonary involvement. The biopsy showed a lymphoid infiltration of the tissue with typical features of extranodal marginal zone B-cell lymphoma of MALT-type (Figure 2), which was confirmed by a national reference centre for lymphoid malignancies (Department of Pathology, Luebeck). However, a CT scan of the neck performed the next day failed to demonstrate pathological subglottic findings, only showing a discrete enhancement between the superior trachea and the esophagus (Figure 3). Clinically, the patient's stridor improved significantly after the steroid bolus but only temporarily. A bone-marrow biopsy and a CT of the abdomen were negative. The esophago-gastroscopy showed obvious signs of reflux disease and ruled out a diverticulum; gastric biopsies were negative for associated gastric MALToma or *Helicobacter pylori*. A repeat bronchoscopy was performed about a week later and confirmed the findings of the first examination. On CT scan there was no cervical or mediastinal lymphadenopathy, and the patient was finally staged IE according to the Ann-Arbor-classification. The patient was referred to an external hematological center where he underwent four cycles of CHOP-R-chemotherapy (cyclophosphamide, doxorubicin, vincristin, prednisolone plus rituximab), which were well-tolerated. The patient received extensive post treatment

Table I. Review of reported laryngeal MALT lymphoma.

| Author                 | Patient gender | Patient age (years) | Localization | Side       |
|------------------------|----------------|---------------------|--------------|------------|
| Diebold, 1990 (2)      | Male           | 60                  | Supraglottic | Left       |
| Kobayashi, 1992 (3)    | Female         | 44                  | Subglottic   | right      |
| Hisashi, 1994 (11)     | Male           | 66                  | Glottic      | Anterior   |
| Kato, 1997 (13)        | Female         | 54                  | Supraglottic | Not stated |
| De Bree, 1998 (15)     | Female         | 36                  | Supraglottic | Right      |
| Usui, 2000 (20)        | Female         | 25                  | Supraglottic | Left       |
| Fung, 2002 (8)         | Male           | 78                  | Supraglottic | Left       |
| Puig, 2002 (17)        | Female         | 79                  | Subglottic   | Right      |
| Caletti, 2003 (10)     | Male           | 57                  | Supraglottic | Right      |
| Kuhnt, 2003 (16)       | Female         | 56                  | Supraglottic | Left       |
| Kania, 2005 (9)        | Male           | 46                  | Supraglottic | Left       |
| Andratschke, 2005 (14) | Male           | 58                  | Subglottic   | Dorsal     |

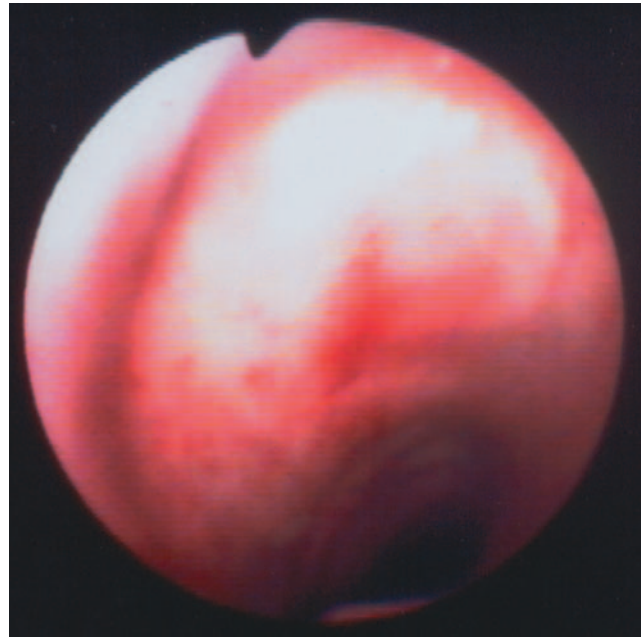


Figure 1. The initial view of the subglottic lesion during bronchoscopy.

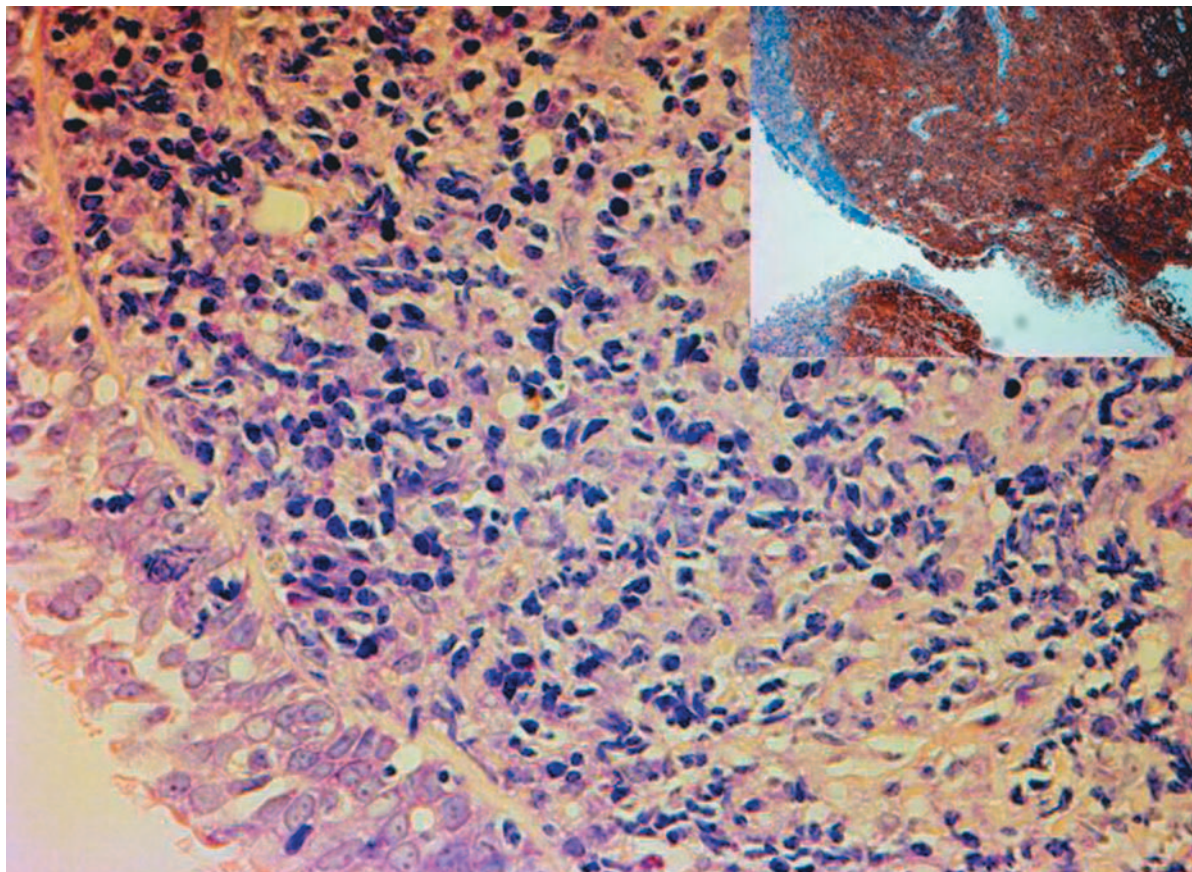


Figure 2. Lower epithelial surface: the histology shows extended pleomorph lymphoid infiltration with single plasma cells (Giemsa, x400) and with evident immunohistochemical CD20 staining (AntiCD20, x100).

follow-up workup including CT scan of neck and thorax, abdominal ultrasound as well as bronchoscopy with a histological examinations of sample biopsies at three, ten, and fifteen months, with no sign of recurrence or a second lesion.

## Discussion

We present a case of a 62-year-old patient with dry cough and stridor who showed a subglottic lesion in bronchoscopy. This lesion was not apparent in the CT scan, probably due to a bolus administration of steroids the day before. The diagnostic staging revealed no other organ or systemic involvement. The chemotherapeutic approach with a CHOP-R-regimen was successful; the event-free period has lasted for more than 15 months.

Gastric lesions are the main manifestation of extranodal marginal zone lymphoma of the MALT-type. Non-gastric processes are infrequent but reported for most organs, however with no defined epidemiological basis. The analysis of extranodal non-gastrointestinal MALT lymphoma show a peak incidence in the 6th and 7th life decade (4, 5); females may outnumber males at a ratio of 3 to 1 (4), or less (5). In a literature review of lymphoproliferative cases of the larynx, Horny found a slight male dominance of 1.3:1 and a median age of 58 years (6). The results of an extensive literature review considering only laryngeal MALT lymphoma are shown in Table I.

Our patient reported typical obstructive symptoms of upper airway with hoarseness of voice, cough, dyspnea, and dysphagia. Signs of general health afflictions or typical B-symptoms of hematological diseases are rare and were not observed in our patient. In most cases reported in literature, there was no additional lymphadenopathy in the head and neck region. Bone-marrow involvement was never found in cases of laryngeal MALT lymphomas, while 16% of non-gastrointestinal MALT lymphoma of other organs showed bone marrow infiltrates and this systemic disease (5). An esophagogastroscope and biopsies for *Helicobacter pylori* are advocated because up to one third of primarily non-gastrointestinal MALT lymphoma also demonstrate gastric lesions (4).

Organized lymphoid tissue with typical MALT features was found exclusively in false vocal folds but not in the subglottic region in a cadaver study by Kutta and co-workers (7). It was apparent that the MALT pattern lymphoid tissue is frequent in children and adolescents (90 to 100% positive findings) with a obvious decreasing rate in upper age groups. These results are in contrast to Fung and colleagues who stated that the larynx is free of native lymphoid tissue and a chronic inflammation like *Helicobacter pylori* (HP) gastritis might induce pathological histology as a precursor of MALToma (8). This is supported by a case of supraglottic lymphoma that was accompanied by reflux (9). Caletti and colleagues reported a patient with a

laryngeal MALToma with an identical concomitant lymphoma clone in the stomach and a *Helicobacter pylori* infection (10). After the first course of HP eradication therapy, the laryngeal lesion also disappeared. Horny described a ratio of four to one for supraglottic versus subglottic manifestations in laryngeal manifestation of lymphoproliferative diseases (6). These data suggest that inflammatory processes are involved in most instances of supraglottic lymphomas. Furthermore, Horny mentioned a left-right ratio of 2 to 1 in accordance with the typical anatomic feature of a slightly left deviation of the cervical part of the human esophagus. The relative infrequency of subglottic MALT lymphoma could be explained by a functional mechanism of the glottis as a mechanical barrier to prevent the spread of inflammatory processes per continuitatem from the afflicted esophagus; the conus elasticus may be an evident obstacle. Nevertheless, the individual predisposition in our case and in most cases is unclear. It is not well-understood what mechanism leads to the development of the MALT-type lymphoma in patients with an HP-positive gastritis in the stomach and gives rise to laryngeal MALT-type lymphoma in patients with HP-positive gastritis with reflux disease. It is a matter of speculation that a clonal lymphoid cell population or an "antigenic" trigger are spread *via* the blood. Dabaja and colleagues showed a gastric association in one third of primarily non-gastrointestinal multifocal presentations of MALT-type lymphoma (4).

There are reports of glottic or tracheal MALT lymphoma that were associated with coexistent squamous cell carcinoma of the mid-esophagus (8), larynx (11) and lung (12). However, the association and etiology of such different tumors need to be clarified further.

Non-Hodgkin's lymphoma of low grade MALT-type lymphoma of the upper airway are sensitive to a variety of therapeutic approaches. There are reports of conventional or laser excisions with the intention of a debulking procedure combined with *Helicobacter pylori* eradication (9), chemo- (3, 13), radiotherapy (8, 11, 14-17), or combined radiochemotherapy (2). We critically judge the surgical approach alone because of the functional defects set by this therapy. Partially excised, primarily misdiagnosed supraglottic MALT lymphoma recurred and was then successfully treated with radiotherapy after a debulking procedure (15). It has to be emphasized that surgery needs to be performed frequently in order to keep the airway open (14). Moderate dose radiotherapy shows favorable outcome in localized MALToma (18) and may be applied without significant side-effects in cases with laryngeal involvement (16). Disease-free periods of more than two years are reported. There are some reports suggesting the use of CHOP or CHOP-like chemotherapy, but Kato *et al.* (13) presented a case of a supraglottic MALT lymphoma, where two cycles of CHOP seemed to be ineffective; the final switch to radiotherapy with 30 Gy led to successful tumor elimination with long lasting remission. A CHOP-regimen with additional

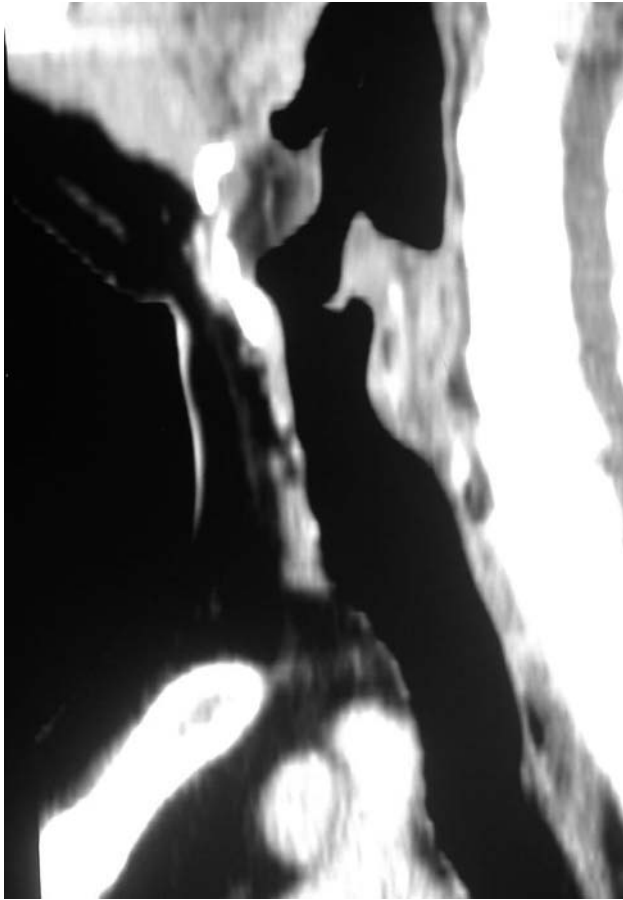


Figure 3. The reconstructed CT of the neck one day after the cortisone administration demonstrates only a very slight subglottic enlargement.

monoclonal anti-CD20-antibody, comparable to our case, was administered to a laryngeal Non-Hodgkin's lymphoma without features of MALT; complete remission was achieved for more than a year (19).

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