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(Citation)

Acta Oto-Laryngologica Case Reports, 3(1):47-51

(Issue Date)

2018

(Resource Type)

journal article

(Version)

Version of Record

(Rights)

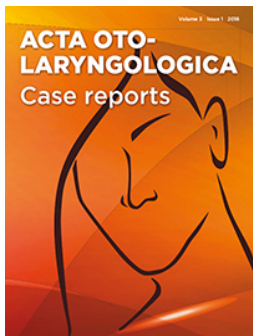
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To cite this article: Natsumi Uehara, Naoki Otsuki, Hirotaka Shinomiya, Keiichiro Uehara & Ken-ichi Nibu (2018) Mucosa-associated lymphoid tissue lymphoma of parotid gland with involvement of subglottis and trachea, Acta Oto-Laryngologica Case Reports, 3:1, 47-51, DOI: [10.1080/23772484.2018.1532294](https://doi.org/10.1080/23772484.2018.1532294)

To link to this article: <https://doi.org/10.1080/23772484.2018.1532294>



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Published online: 08 Dec 2018.



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CASE REPORT



Mucosa-associated lymphoid tissue lymphoma of parotid gland with involvement of subglottis and trachea

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ABSTRACT

Although it is well recognized that the salivary glands may acquire Mucosa-associated lymphoid tissue (MALT) lymphoma as a result of Sjögren syndrome (SS), involvements of subglottis and trachea are rare. A 78-year-old woman was referred to our hospital for an enlarged mass of the right parotid area with a history of SS for 7 months. Two weeks after the first visit, she presented with the complaint of stridor and difficulty in breathing. Laryngoscopy revealed the stricture of subglottic space due to the nodular submucosal mass. She was emergently admitted and underwent tracheostomy. Biopsies of the tracheal mucosa and subglottic nodular submucosal mass were pathologically diagnosed as MALT lymphoma. After 6 courses of rituximab plus CHOP (R-CHOP), all lesions disappeared and tracheal stoma were successfully closed. Although MALT lymphoma of upper respiratory tract is extremely rare, respiratory tract should be examined in the patients of parotid lymphoma associated with SS.

ARTICLE HISTORY

Received 13 July 2018
Revised 30 August 2018
Accepted 2 October 2018

KEYWORDS

MALT lymphoma; subglottis; trachea; Sjögren syndrome; parotid gland

Introduction

Mucosa-associated lymphoid tissue (MALT) lymphoma is an extranodal low-grade B-cell lymphoma, first described by Isaacson and Wright in 1983 [1]. This tumor involves a wide variety of extranodal sites, gastrointestinal tract, thyroid and salivary gland, in the setting of chronic local inflammatory or autoimmune disorders, such as Sjögren syndrome (SS) [2]. It is well known that MALT lymphoma often occurs in the parotid gland of the patients with SS [3]. However, MALT lymphoma involving the larynx and trachea is extremely rare regardless of primary or secondary dissemination. Here, we report a case of parotid MALT lymphoma with SS presented as stridor due to subglottic and tracheal involvement and discuss the clinical feature and the management of MALT lymphoma involving the respiratory tract.



Case report

A 78-year-old Japanese woman was referred to our hospital with a complaint of painless and slowly progressive mass in the right parotid gland. She had a history of SS for 7 months, but did not have

symptoms, such as fever, weight loss, or night sweat. Physical examination revealed an elastic soft, mobile, and non-tender mass in right parotid area measuring 52 × 47 mm in diameter. She had neither facial weakness nor cervical lymphadenopathy. Blood examination showed no abnormality except for slightly increased serum interleukin-2 receptor (IL-2R) level (530: normal range <500). Both anti-SS-A and SS-B antibody test were positive.

Magnetic resonance image (MRI) revealed a round mass with low signal intensity on T1-weighted image and intermediate and low signal intensity on T2-weighted image in the right parotid gland. Both sides of the parotid gland accompanied with multiple small foci of high signal intensity area on T2-weighted image (Figure 1(A)). Fine-needle aspiration cytology from the parotid mass detected small lymphocytes without cytological atypia. From these findings, we suspected malignant lymphoma of parotid gland and scheduled open biopsy of the parotid mass.

Two weeks after the first visit, she visited our department with a complaint of stridor and slight inspiratory dyspnea. Laryngoscopy revealed the stricture of subglottic space caused by nodular submucosal

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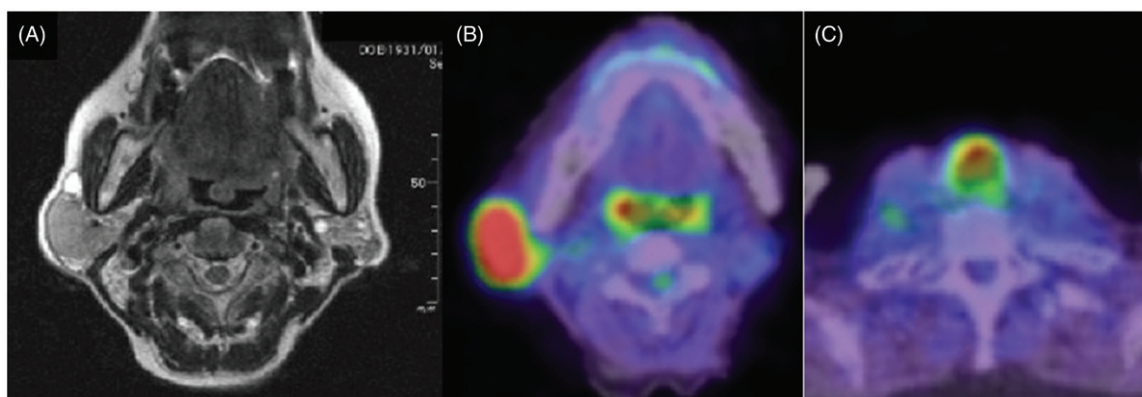


Figure 1. Magnetic resonance imaging showed a round mass in the right parotid gland. Both sides of the parotid gland accompanied with multiple small foci of high signal intensity area on T2-weighted image ((A) axial image) 18FDG-PET showed an abnormal uptake in right parotid gland (B) and subglottic space (C).

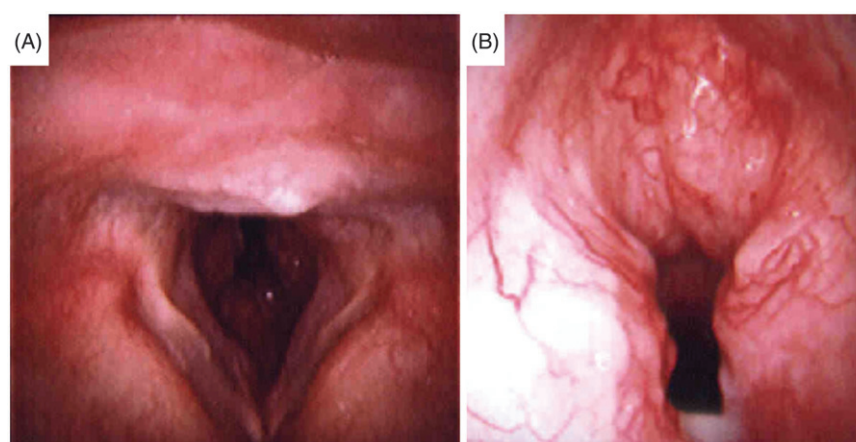


Figure 2. Laryngoscopy revealed the stricture of subglottic space caused by granulomatous lesion of subglottis. (A) The findings through the retrograde laryngoscopy through tracheostoma. Tracheal mucosa was edematous and subglottic space was narrowed by nodular submucosal mass (B).

mass of subglottis and trachea (Figure 2). She was admitted emergently to our department and underwent tracheostomy under local anesthesia for the relief of choking. Subglottic lesion was retrogradely observed by the flexible laryngoscope through the tracheal stoma. Tracheal mucosa was edematous and subglottic space was narrowed by nodular submucosal mass. Biopsies of the tracheal mucosa and subglottic lesion were performed. Incisional biopsy of the right parotid mass was also performed 2 d after tracheostomy. The tumor was elastic and smooth on the surface.

Histopathological examinations of tracheal, subglottic, and parotid specimen revealed sheets of infiltrating small to medium lymphocytes that have slightly irregular nuclei (Figure 3(A,B)). Immunohistochemical analysis of these tumor cells indicated uniform presence of B-cell markers CD20, the absence of CD10, CD5, and cyclinD1 (Figure 3(C)). Given these findings, the diagnosis of extranodal marginal zone lymphoma arising from MALT

was made. The neoplastic lymphoid cells showed diffuse positive staining for Epstein-Barr virus (EBV) early RNA (EBER) by in situ hybridization (Figure 3(D)). A staging workup of 18FDG-PET and CT scan of whole body showed no abnormalities except for the right parotid gland, larynx and trachea (Figure 1(B,C)), and she was diagnosed as having stage II E (Ann-Arbor-classification) MALT lymphoma. She underwent six courses of chemotherapy with rituximab plus CHOP (R-CHOP); cyclophosphamide (625 mg/m^2), doxorubicin (42 mg/m^2), vincristine (1.2 mg/m^2), prednisolone (100 mg/body), and rituximab (375 mg/m^2). Considering her age, dosages were reduced to 5/6 of standard dosages except for prednisolone and rituximab. After the first course of chemotherapy, the right parotid mass decreased obviously in size and the laryngo-tracheal stenosis was remarkably improved (Figure 4). Complete remission was obtained after six courses of chemotherapy with R-CHOP and tracheal stoma was successfully closed

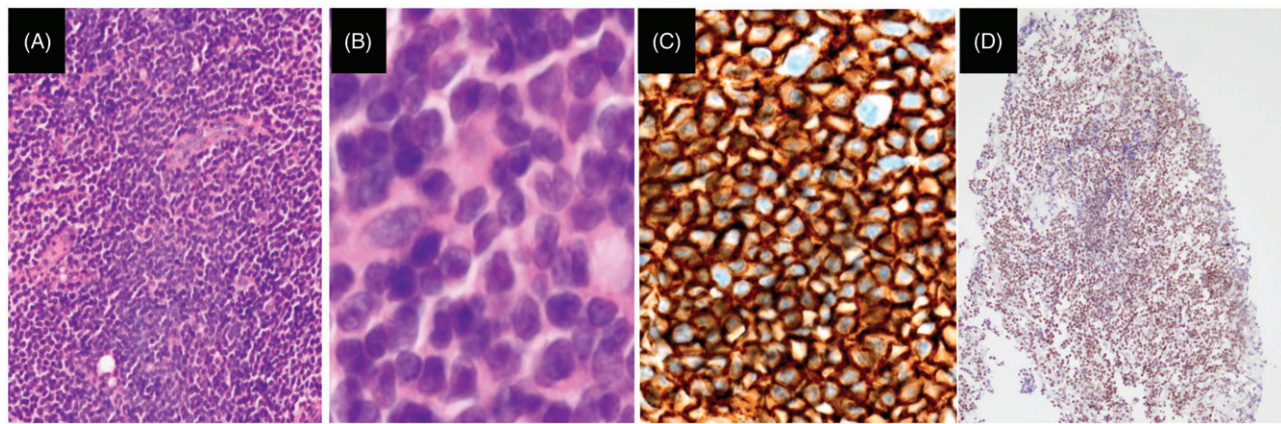


Figure 3. Histological examinations of biopsied specimen revealed sheets of infiltrating small to medium lymphocytes have slightly irregular nuclei ((A) HE stain, $\times 40$, (B) $\times 400$). Immunohistochemical analysis shows that these tumor cells indicated uniform presence of B-cell markers CD20 ((C) CD20, $\times 200$). EBER *in situ* hybridization analysis shows that these tumor cells are positive for EBV ((D) $\times 20$).

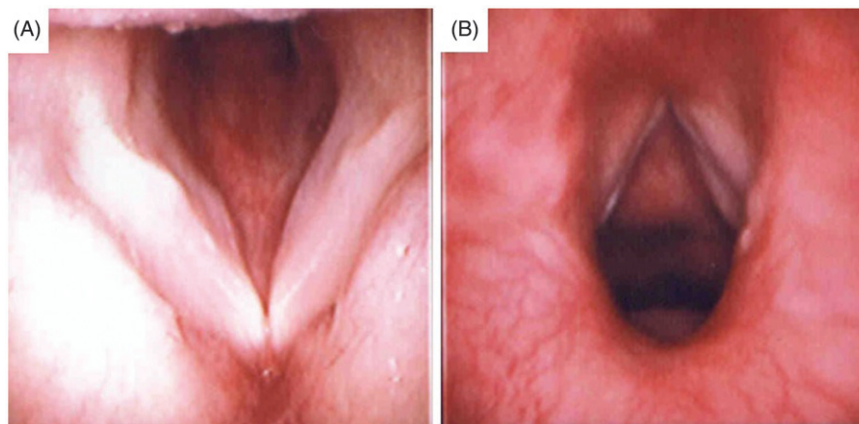


Figure 4. Finding of trachea and subglottic space after the first course of chemotherapy. Laryngoscopic view (A) and retrograde view through tracheostoma (B). The laryngo-tracheal stenosis was remarkably improved.

Table 1. Review of reported cases with subglottis and/or trachea MALT lymphoma.

Reference (year)	Age/sex	Location	Treatment	Comorbidity	Follow-up
[6]	46/M	Sub	S + C	–	NA
[7]	44/F	Sub, Tra	T + C	–	NER 12 M
[8]	79/F	Sub	RT	–	NED 8 M
[9]	58/M	Sub	T + RT	–	NER 12 M
[12]	62/M	Sub	C	–	NED 15 M
[10]	61/F	Sub, Tra	S	SS	NER 4 M
[11]	41/F	Sub	C + RT	RA	NER 10 M
[12]	73/F	Sub	RT	–	NA
[Current study]	78/F	Sub, Tra, Par	T + C	SS	NED 61 M

NA: not available; Tra: trachea; Sub: subglottis; Par: parotid gland; RT: radiotherapy; S: surgery; T: tracheostomy; C: chemotherapy; M: months.

2 months after the completion of the treatment. She has been alive without disease for 61 months after definitive diagnosis.

Discussion

MALT lymphoma is an extranodal low-grade B-cell lymphoma and most cases occur in adults with a

median age of six decades and slight female preponderance [2]. Although about 60% of all MALT lymphoma occur in the gastrointestinal tract (especially the stomach), it has also been described in non-gastrointestinal sites, such as salivary gland, conjunctiva, thyroid, orbit, lung, breast, kidney, skin, liver, and prostate. It generally arises in lymphoid tissue that has been acquired as a result of some pre-existing disorder, e.g. *Helicobacter pylori* colonization in the stomach, follicular bronchiectasis in the lung, autoimmune disease in the salivary gland (SS) and thyroid gland (Hashimoto's thyroiditis) [3]. MALT lymphoma is characterized by localization to the primary site for a long time and indolent clinical course, and the majority of patients present with clinical stage I or II disease at the time of first diagnosis [4]. However, several investigators previously demonstrated that patients with MALT lymphoma of the head and neck area have a relatively high risk for multifocal disease and/or lymph node involvement and recurrence [5].

Thieblemont et al. studied 165 patients with non-gastrointestinal MALT lymphoma and they documented dissemination of the disease at the first diagnosis in 48% of cases [4].

MALT lymphoma of the trachea and larynx are extremely rare. To date, only eight cases with subglottic involvement have been reported in the literature according to PubMed search (Table 1) [2,6–12]. Most cases were localized in the primary sites and their prognosis was favorable. Out of eight cases of subglottic MALT lymphoma, only two cases were involved in the trachea and no case involved in the other non-respiratory tract. In our case, the primary parotid MALT lymphoma with SS involved subglottis and trachea. Kobayashi et al. reported a case with MALT lymphoma of subglottis and trachea similar to our case, but their case was localized to one extranodal site and had no autoimmune disease [7]. On the other hand, Korst reported a case of primary MALT lymphoma of the subglottic airway in a patient with SS, which resembled a benign, cicatricial subglottic stenosis, was successfully managed by surgical resection with laryngo-tracheal reconstruction [10].

The close relationship between SS and malignant lymphomas has been known since 1963. SS has the strongest link with non-Hodgkin's lymphoma (NHL) compared with other autoimmune diseases, such as systemic lupus erythematosus (SLE) and rheumatoid arthritis [5,13]. Voulgarelis et al. reported that NHL had 4.3% prevalence in patients with SS, and salivary glands were the most commonly affected site [14]. Twenty percent of the patients with SS displayed involvement of more than one extranodal site at first diagnosis, indicating that these lymphomas preferentially migrate to other mucosal sites. Thereby complete staging procedures are recommended in patients who have MALT lymphoma with SS. Moreover, it is well recognized that lymphoproliferative disorders in lungs, such as lymphocytic interstitial pneumonia, pseudolymphoma often observed in patients with SS [15]. Recently, almost these diseases are thought to be corresponded to MALT lymphoma and have known as bronchial-associated lymphoid tissue (BALT) lymphoma [16,17]. In this case, the parotid MALT lymphoma was not localized and involved larynx and trachea 7 months after the first noted SS.

Diss et al. reported that EBV was identified in 3 of 45 parotid gland MALT lymphomas [18]. The malignant cells were positive for EBV, suggesting the positive role of the virus in tumor progression.

There is no established management of the MALT lymphomas of subglottis and/or trachea and several

treatment options exist, such as surgical resection, laser excision, radiation, and chemotherapy (Table 1). In clinical stage I or II, MALT lymphomas can be considered curable with local therapy alone, either surgery and/or radiotherapy. Combined chemotherapy may be considered in patients with disseminated or recurrence disease [2,5]. Recently, excellent result was reported by using rituximab that is anti-CD20 antibody [3]. Rituximab also has been shown to be a viable therapeutic agent in the treatment of SS either with or without MALT lymphomas [13]. On the other hand, several investigators demonstrated the less favorable outcome in non-gastrointestinal MALT lymphoma, especially in the head and neck area [19]. Wenzel et al. reported that 15 out of 36 patients (43%) with MALT lymphoma in the head and neck area experienced disease recurrence [20]. Out of these 15 patients with disease recurrence, 11 patients underwent initially local therapy only. Of note, the patients with parotid MALT lymphoma had a high tendency of recurrence in other non-gastrointestinal sites. Thus, long-term careful periodic evaluation is recommended.

Conclusions

In summary, we reported a case of parotid MALT lymphoma associated with SS involving upper respiratory tract. Six courses of R-CHOP resulted in complete response with no recurrence of disease for five-years. Although MALT lymphoma of upper respiratory tract is extremely rare, respiratory tract should be examined in the patients of parotid lymphoma associated with SS.

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