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## Case Report

# Lymphoepithelial carcinoma of the submandibular gland in a Japanese male: A case report <sup>☆,☆☆</sup>

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## ABSTRACT

Lymphoepithelial carcinoma of the submandibular gland is an extremely rare condition; therefore, no clear clinical features or established treatment is available for this. A 58-year-old Japanese man who came to our hospital with the complaint of swelling of the left submandibular region was diagnosed with stage IVa, T4aN2bM0 lymphoepithelial carcinoma of the submandibular gland. We also examined the relationship between the tumor and Epstein–Barr virus by Epstein–Barr virus encoded ribonucleoprotein in situ hybridization. The patient was treated by performing segmental mandibulectomy, neck dissection, mandibular reconstruction, and adjuvant chemoradiotherapy. After 2 years of treatment, good progress has been observed in the patient without any signs of recurrence. Here, we have reported the treatment of a patient with lymphoepithelial carcinoma of the submandibular gland using literature review.

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## Introduction

Lymphoepithelial carcinoma (LEC) is defined as anaplastic carcinoma accompanied with non-neoplastic lymphocytic infiltration. LEC most commonly arises in the upper pharynx, whereas primary onset in the submandibular gland is rare [1]. LEC as salivary gland cancer is a rare histological type.

LEC of the upper pharynx is associated with the Epstein–Barr virus (EBV), and because it has high radiosensitivity, radiation-based treatment is performed. However, there is no established treatment for LEC of the submandibular gland and administering radiation-based treatment or to perform

surgery is controversial. We report our experience of a case diagnosed as having LEC of the submandibular gland, in which good progress was obtained by performing surgery with segmental mandibulectomy, neck dissection, and mandibular reconstruction, followed by chemoradiotherapy (CRT).

## Case report

A 58-year-old Japanese male patient had noticed swelling of the left submandibular region over the past 3 years. The swelling increased before 3 months, and the patient consulted

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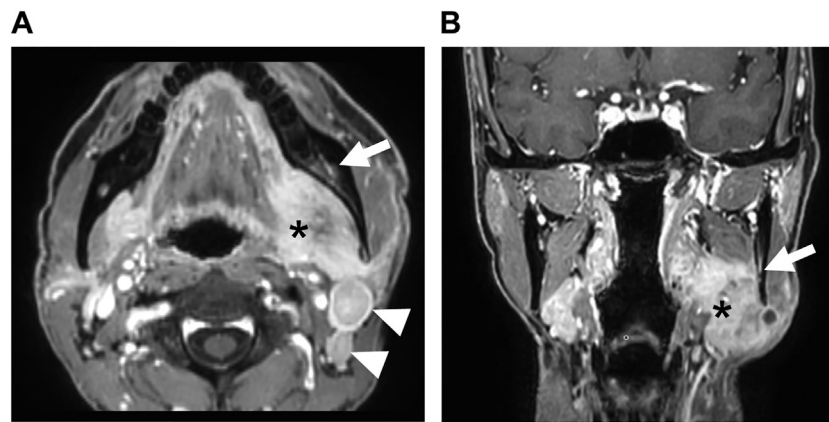
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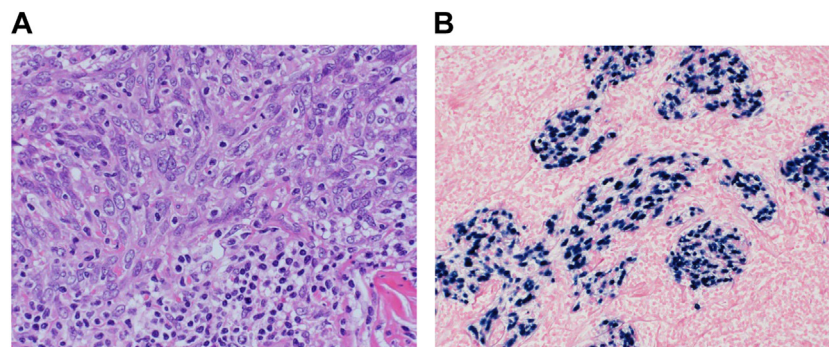
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**Fig. 1 – Contrast-enhanced magnetic resonance imaging (MRI) during initial examination. A tumor with unclear border surrounding the inferior border of the left mandible (\*), with several enlarged lymph nodes in the left mandibular region (arrow head), and contrast-enhancement in the mandibular bone (arrow) were observed.**

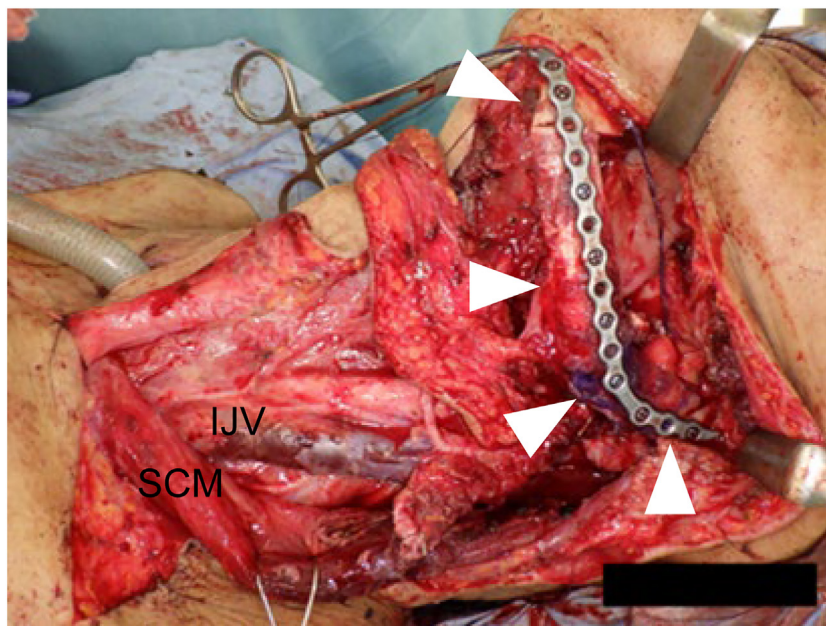


**Fig. 2 – Pathological findings of the submandibular tumor. (A) Haematoxylin and eosin staining (×400), (B) EBER-ISH (×100). (A) Irregular and uneven alveolar invasion of a poorly differentiated tumor was observed extending in insular form with lymphoid stroma. (B) The majority of tumor cells exhibited EBER-ISH signal.**

our department. No previous medical history, family history, or smoking habit was recorded. There was no history of international travel or residence. The physical findings at the initial examination revealed a solid tumor with poor mobility in the left submandibular region. There were no particular findings in the oral cavity, nasal cavity, nasopharynx, oropharynx, hypopharynx, or larynx. On contrast enhanced magnetic resonance imaging (MRI), contrast-enhancement was observed in the mandible. The border with the soft tissue surrounding the left submandibular region was indistinct, and several enlarged lymph nodes were observed as the tumor spread to encompass the mandible (Fig. 1). Positron emission tomography-computed tomography (PET-CT) did not reveal any specific uptake other than that in the existing lesion, and distal metastasis was not observed. Fine-needle aspiration cytology did not lead to diagnosis. Moreover, on the basis of histology of the left submandibular adenoma, irregular and uneven alveolar invasion of a poorly differentiated tumor was observed extending in an insular form with lymphoid stroma (Fig. 2A). Immunohistochemically, the tumor cells were positive for cytokeratin AE1/AE3, epithelial membrane antigen (EMA), CK5/6, and p40 and negative for smooth muscle antibody (SMA). Furthermore, EBV encoded ribonucle-

oprotein in situ hybridization (EBER-ISH) of the tumor tissue was positive (Fig. 2B). Upon diagnosis of LEC of the left submandibular gland: T4aN2bM0 Stage IVA (the 8th edition of the Union for International Cancer Control TNM staging system), surgery and adjuvant CRT were planned. For the surgical procedure, we performed tracheostomy, followed by segmental mandibulectomy and neck dissection (level I-V) under general anesthesia. The primary tumor had spread so as to encompass the inferior border of the mandible; therefore, osteotomy of the mandible was performed between the second and third lower left teeth with the ramus of the mandible, which was resected en bloc with the tumor. The mandible defect site was reconstructed using a free fibular flap and a titanium plate (Fig. 3), and end-to-end anastomosis of the peroneal and superior thyroid artery was observed. The operative duration was 12 h 31 min, and the volume of blood loss was 320 mL. Regarding the resected specimen, a tumor of 35 × 40 × 64 mm in size surrounding the mandible with neural invasion was observed. The resected stump was negative. Four lymph node metastases at level II were observed.

Postoperative progress: The tracheal cannula was removed on postoperative day 7, and oral ingestion was recommenced on postoperative day 12. The wound progress was good, and



**Fig. 3 – Surgical outcomes.** Osteotomy of the mandible was performed between the second and third lower left teeth with the ramus of mandible, which was resected en bloc with the tumor. The mandible defect site was reconstructed using a free fibular flap and titanium plate (arrow head).

the amount of ingestion was stable; thus, the patient was discharged on postoperative day 26. CRT (66 Gy/33 Fr combined with weekly cis-diamminedichloroplatinum II (CDDP) 40 mg/m<sup>2</sup> 6 times) was performed from postoperative day 39; however, no serious adverse events were observed. Currently, 2 years after surgery, the patient has had no recurrence or metastasis, is eating a normal diet, and is progressing well.

## Discussion

LEC is defined as an anaplastic carcinoma accompanied by clear histological lymphocytic infiltration [1]. The most common site of LEC onset is the upper pharynx. In the head and neck regions, LECs of the salivary gland have been reported; however, the parotid gland is commonly affected [2]. Furthermore, among malignant tumors of the salivary glands, the incidence of LEC is low at 0.4% [3]. Zhan et al. reported that although there is no significant difference in overall survival between submandibular and parotid gland cancers, there are clinical differences. Specifically, there is a higher incidence of submandibular LECs among American Indians, Aleutians, Eskimos, and Asians, with more patients presenting with T3-T4 lesions and a higher frequency of local metastasis [4].

Pathologically, it resembles nasopharyngeal LEC, and the diagnosis requires exclusion of the nasopharyngeal primary. In this case, nasopharyngeal fiber imaging, contrast-enhanced MRI, and PET-CT were performed to confirm the absence of lesions in the nasopharynx. Immunohistologically, LEC is positive for epithelial markers, such as AE1/AE3, CK5/6, p40, p63, and EMA [2]. EBV is thought to be involved in the mechanism of carcinogenesis in LEC, EBV in tumor cells was identified

through EBER-ISH and has been reported to be a useful prognostic factor [5].

While past reports have described clinical information, such as the prognosis and treatment methods of LEC of the submandibular gland, to the extent of our search of the literature, there were only 10 cases [1,3,6–9]. The 11 cases included in these reports with this case are presented in Table 1. The relationship between EBV and LEC of the submandibular gland was not mentioned in 2 cases; however, in 9 cases, EBER-ISH was performed and had positive results in 88.9% (8/9 cases). Whaley et al. reported that among 16 cases of salivary gland LEC, the EBER positivity rate was 46.2% (6/13 cases) in the parotid gland and 66.7% (2/3 cases) in the submandibular gland [6]. This suggests that the EBER positivity rate might be higher in the submandibular gland LEC, indicating a stronger involvement of EBV in the development of the LEC.

Regarding treatment and prognosis, although patients with a short observation period were included, LEC of the submandibular gland was treated surgically in all patients. There was recurrence-free survival in 90.9% (10/11 patients), death in 1 patient, which was due to another illness; thus, the prognosis of patients who underwent surgery can be good. Epidemiology and prognosis analysis of LEC showed that disease-specific survival rate of primary LEC in the head and neck other than the upper pharynx is significantly improved by surgery [10]. The treatment of LEC of the upper pharynx is based on radiotherapy; however, if resectable, surgery can be an option for LEC of the submandibular gland. On preoperative contrast-enhanced MRI, our patient presented with contrast enhancement in the bone, the border with the surrounding soft tissue was indistinct, and the mandible was surrounded; therefore, segmental mandibulectomy was needed to resect the tumor en bloc.



**Table 1 – Clinical features and outcomes of patients with lymphoepithelial carcinoma of the submandibular gland since 1995.**

Author	Region	Age	Sex	Side	T	N	Stage	EBER-ISH	Treatment	Status
Leung SY [1]	Hong Kong	41	M	NR	2	0	Stage II	positive	Surgery + RT	Alive, 5.2 y
		32	M	NR	2	1	Stage III	positive	Surgery + RT	Alive, 3 m
Jang SJ [7]	Korea	16	M	L	2	2b	Stage IVA	NR	Surgery	Alive, 10 m
Kim YJ [8]	Korea	71	F	R	2	0	Stage II	positive	Surgery	Alive, 5.0 y
Sairin ME [3]	Malaysia	70	F	R	2	0	Stage II	NR	Surgery	Alive, 1.0 y
Whaley RD [6]	USA	18	F	R	2	1	Stage III	positive	Surgery	Alive, 6.6 y
		46	M	R	3	0	Stage III	positive	Surgery	Alive, 8.0 y
		77	F	L	2	1	Stage III	negative	Surgery	DFOC, 4.4 y
Chou CT [9]	Taiwan	58	F	NR	NR	Stage III	positive	Surgery + RT	Alive, 6.3 y	
		12	M	NR	NR	Stage IVA	positive	Surgery + RT	Alive, 11.7 y	
Present case	Japan	58	M	L	4a	2b	Stage IVA	positive	Surgery + CRT	Alive, 2.0 y

EBER-ISH, EBV encoded ribonucleoprotein in situ hybridization; y, year(s); m, month(s); NR, not reported; RT, radiation therapy; DFOC, death from other causes.

LEC of the salivary gland with tumor diameter  $\geq 3$ cm and/or accompanied by several lymph node metastases, postoperative RT improves the survival and local control rates [11]. In the present case, 4 lymph node metastases and neural invasion were observed; therefore, considering the high risk of recurrence, we performed CRT, which is a more intense treatment than RT. We believe that the significance of adding chemotherapy to postoperative RT for LEC of the submandibular gland should be examined in future studies. Our patient required reconstructive surgery but is alive and recurrence-free, and has maintained a quality of life after treatment; therefore, our treatment policy was appropriate.

## Patient consent

Written informed consent for the publication of this case report was obtained from the patient.

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