



# Lymphoepithelial Carcinoma of the Larynx: A Case Report

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## Abstract

Lymphoepithelial carcinoma (LEC) is a rare malignancy that histologically resembles nonkeratotic nasopharyngeal carcinoma. Most head and neck LECs occur in the nasopharynx and are associated with Epstein–Barr virus infection, and non-nasopharyngeal LECs are extremely rare. Herein, we report a case of supraglottic LEC. The patient was a 73-year-old man in whom a laryngeal mass was incidentally detected during treatment for another disease. Computed tomography and magnetic resonance imaging revealed tumor invasion of the thyroid cartilage and a metastatic left cervical lymph node. The histological diagnosis was EBER(+) LEC, and the final diagnosis was supraglottic carcinoma (LEC, cT4aN2aM0). The patient was treated with neoadjuvant chemotherapy followed by surgery. At present, 8 months after the surgery, the patient remains under observation with no postoperative treatment, and no evidence of recurrence has been observed. In general, virus-associated cancers often have a better prognosis than nonvirus-associated cancers; however, the association between the prognosis of non-nasopharyngeal LEC and viral infection is currently unclear. Our experience with this case suggests that non-nasopharyngeal LEC could be effectively treated according to the treatment protocol for conventional squamous cell carcinoma of the head and neck with or without viral infection.

## Keywords

- ▶ lymphoepithelial carcinoma
- ▶ Epstein–Barr virus
- ▶ nonkeratinizing nasopharyngeal carcinoma

## Introduction

Lymphoepithelial carcinoma (LEC) is a rare malignancy defined by the World Health Organization as “a poorly differentiated squamous cell carcinoma morphologically similar to nonkeratinizing nasopharyngeal carcinoma (NPC)” and is classified into nasopharyngeal and non-nasopharyngeal types.<sup>1</sup> Nasopharyngeal LECs are associated with viruses such as Epstein–Barr virus (EBV), whereas the viral association of non-nasopharyngeal LECs remains unclear.<sup>2</sup> According to the Head and Neck Cancer Registry, primary LEC of the larynx is extremely rare, with an incidence of 0.036%.<sup>3</sup>

Here, we report a case of EBV-associated non-nasopharyngeal (laryngeal) LEC.

## Case Presentation

**Patient:** A 73-year-old man

**Chief complaints:** sore throat and left-sided neck mass

**Past medical history:** history of surgery for an inguinal hernia

**Family history:** unremarkable

**History of alcohol and cigarette use:** occasional alcohol consumption. He smoked 15 cigarettes a day for ~10 years.

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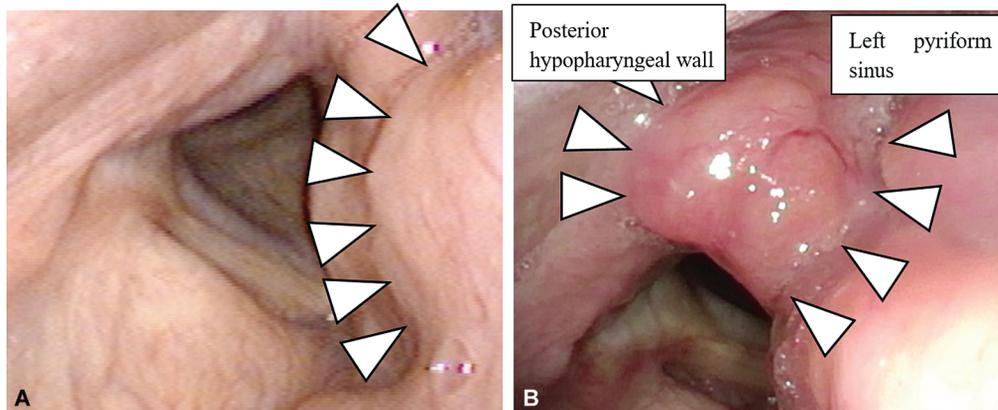
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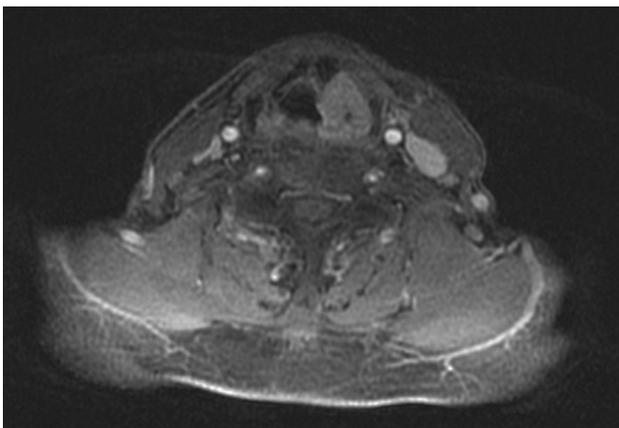
**Fig. 1** Laryngopharyngoscopic images. Arrowheads denote tumors. (A) A lesion was primarily located in the left supraglottic region, extending to the submucosal layer. (B) A mass lesion extending from the pyriform sinus to the postcricoid region of the hypopharynx was observed.

History of present illness: during surgery for an inguinal hernia, a laryngeal mass was incidentally noted during orotracheal intubation for the induction of general anesthesia. Around the same time, the patient became aware of a sore throat and a left-sided neck mass, prompting a visit to his previous physician. The physician conducted an endoscopic examination of the pharynx and larynx and noted an elevated lesion in the left supraglottic region. An endoscopic biopsy of the lesion was performed. The results indicated a suspicion of malignancy, suggesting laryngeal cancer. Consequently, he presented to our department as a new patient for further evaluation and treatment.

Systemic findings at the initial visit: Performance Status 0

Laryngopharyngoscopy at the initial visit: an elevated lesion was observed mainly in the left supraglottic region, extending into the submucosal layer and continuing from the pyriform sinus to the postcricoid region of the hypopharynx (► Fig. 1). The left vocal cord motion was impaired.

Contrast-enhanced magnetic resonance imaging: a 22-mm contrast-enhancing mass was identified in the left supraglottic region, extending into the pyriform sinus and postcricoid region (► Fig. 2).



**Fig. 2** Contrast-enhanced magnetic resonance imaging at the initial visit. A mass lesion with contrast enhancement was located primarily in the supraglottic region, reaching the pyriform sinus.

Contrast-enhanced computed tomography: the mass in the left supraglottic region caused thyroid cartilage destruction and extended into the extralaryngeal space. A round, contrast-enhancing lymph node measuring approximately 43 mm was observed in the left superior and inferior deep neck regions, suggesting lymph node metastasis. No signs of extranodal invasion were observed (► Fig. 3).

Fluorodeoxyglucose (FDG) positron emission tomography: a high FDG uptake consistent with the known left supraglottic mass was observed. High FDG accumulation was observed in the enlarged left neck lymph node. No findings indicated distant metastasis.

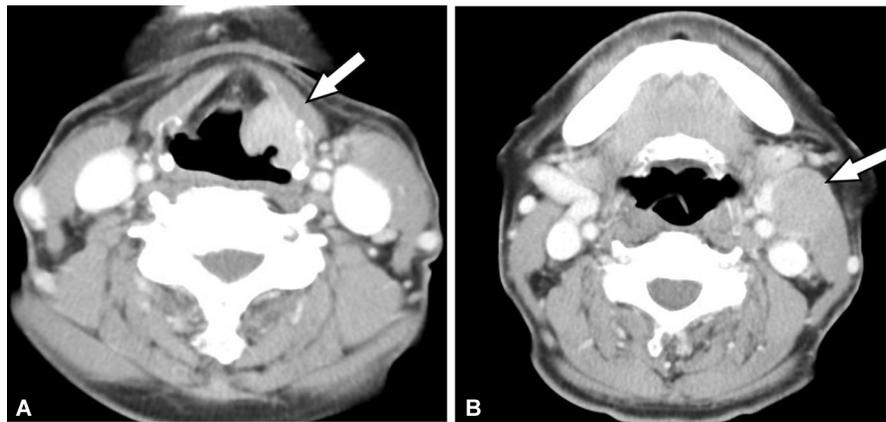
Laboratory findings: general and biochemical blood tests revealed no abnormalities.

Tissue biopsy: a biopsy of the elevated laryngeal lesion was performed via laryngopharyngoscopy. Atypical epithelial hyperplasia with nuclear enlargement and mitotic figures was observed, accompanied by prominent lymphocytic infiltration beneath the atypical epithelium. Immunostaining revealed AE1/AE3(+), p16(+), p63(+), p53(-), and CD56(-) tumor cells surrounded by CD3(+) and CD20(+) lymphocytes. AE1/AE3 and p63 also indicated clear interstitial infiltration. In situ hybridization (ISH) revealed EBER(+) cells.

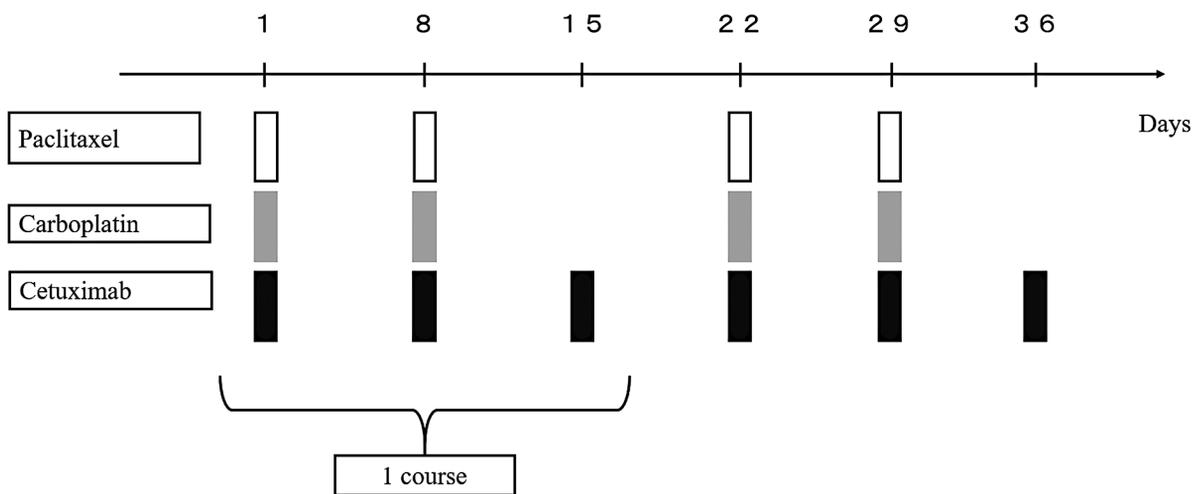
Clinical diagnosis: left supraglottic cancer (left false vocal cord, LEC, cT4aN2aM0, and cStage IVA).

### Progress

Radical surgery was planned, comprising pharyngolaryngoesophagectomy, bilateral neck dissection, and free jejunal autograft reconstruction. However, because surgical preparation required at least 1 month, preoperative chemotherapy was administered to prevent disease progression from affecting surgical eligibility. Because there were no established chemotherapy regimens for LECs, we selected the paclitaxel 100 mg/m<sup>2</sup> (PCE) regimen (paclitaxel 100 mg/m<sup>2</sup>, carboplatin AUC 2, and cetuximab 400 mg/m<sup>2</sup>), commonly used for squamous cell carcinomas. As shown in ► Fig. 4, each PCE course lasted 3 weeks: all three drugs were administered in weeks 1 and 2, with cetuximab alone administered in week 3.<sup>4</sup> Two courses were administered without any serious adverse events (Grade ≥ 3). Treatment response was partial response at the primary lesion and stable



**Fig. 3** Contrast-enhanced computed tomography at the initial visit. (A) The tumor invaded and destroyed the thyroid cartilage, extending into the extralaryngeal space. The arrow denotes the tumor. (B) A 43-mm enlarged lymph node suggestive of metastasis was observed in the left neck. The arrow denotes the enlarged lymph node.



**Fig. 4** PCE regimen administered in our department. PCE, paclitaxel 100 mg/m<sup>2</sup>.

disease at the left cervical lymph node (►Fig. 5). Considering the availability of additional time before surgery, four supplementary doses of cetuximab were administered. The patient underwent pharyngolaryngoesophagectomy, bilateral neck dissection, and free jejunal autograft reconstruction approximately 4 months after diagnosis. Lugol's iodine staining was performed during mucosal incision due to ulcerated mucosal lesions in the left pyriform sinus. During neck dissection, lymph nodes from levels II to IV were removed bilaterally. The metastatic node in the left neck was adjacent to the internal jugular vein but was easily dissected, as the vein was not invaded.

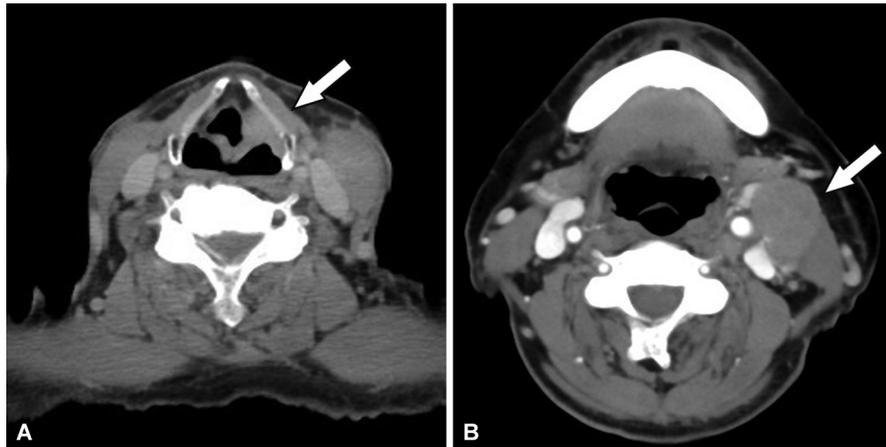
A postoperative permanent specimen revealed atypical epithelial cells displaying an alveolar infiltrative growth pattern, accompanied by necrosis and prominent infiltration of lymphocytes and plasma cells (►Fig. 6). Immunostaining revealed that the tumor cells were negative for CD56, chromogranin A, INSM1, synaptophysin, and p53 and positive for p40, CK14, p63, CK5/6, and p16, with a Ki-67 labeling index of 60%. ISH demonstrated EBER(+) cells and human papillomavirus (HPV)(-) status (►Fig. 7). These findings confirmed the

diagnosis of LEC. The resection margin was negative, and tumor cell invasion of the paraglottic space was observed, with no extralaryngeal extension. Among the cervical lymph nodes, only one left superior deep cervical node—initially suspected of metastasis—tested positive, without extranodal extension. Based on these findings, the postoperative diagnosis was left supraglottic cancer (left false vocal cord, LEC, pT3N2aM0, and pStage IVA).

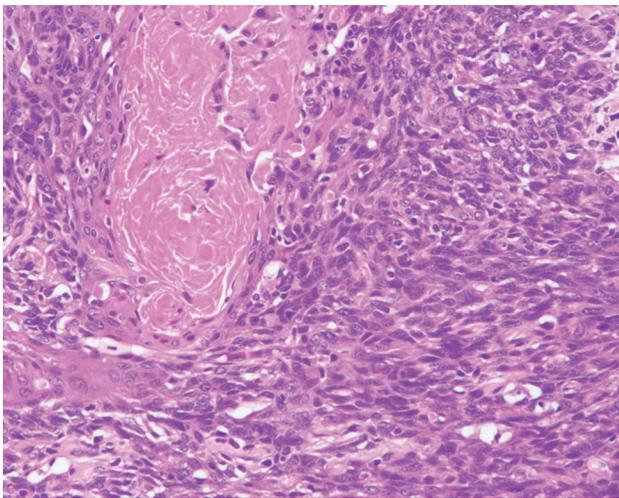
No additional postoperative treatment was administered because the margin was negative and the metastatic lymph node lacked extranodal invasion. The patient remains recurrence-free at 12 months postoperatively.

## Discussion

Most LECs in the head and neck region occur in the nasopharynx, whereas non-nasopharyngeal LECs are extremely rare. The salivary glands account for a relatively large proportion of reported non-nasopharyngeal LECs, whereas other sites, such as the oral cavity, oropharynx, hypopharynx,



**Fig. 5** Contrast-enhanced CT after treatment with the PCE regimen. (A) A reduced size of the primary lesion was observed. The arrow denotes the tumor. (B) The left cervical lymph node was graded as stable disease. The arrow denotes the enlarged lymph node. CT, computed tomography; PCE, paclitaxel 100 mg/m<sup>2</sup>, carboplatin AUC 2, and cetuximab 400 mg/m<sup>2</sup>.



**Fig. 6** Pathological findings of the permanent specimen preparation (hematoxylin and eosin staining,  $\times 200$ ). Atypical epithelial cell growth in an alveolar pattern was observed. Necrosis was also observed, with prominent lymphocyte and plasma cell infiltration.

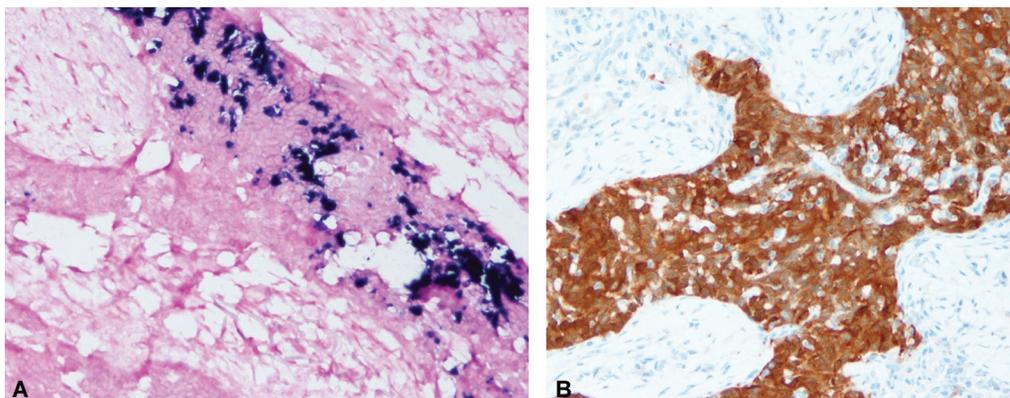
and larynx, represent minor proportions.<sup>2,3</sup> LECs have also been reported in organs outside the head and neck, including

the thymus, lungs, skin, uterine cervix, stomach, gallbladder, urinary bladder, and mammary glands, although all occurrences are extremely rare.<sup>5</sup>

Unlike nasopharyngeal LECs, which are common among individuals of Chinese descent, primary laryngeal LECs are reportedly more common among White men in their 50s to 70s.<sup>2</sup> Although the full spectrum of risk factors remains unclear, it likely includes cigarette and alcohol use. The most common clinical symptoms are dysphonia and dysphagia. LECs tend to invade the surrounding structures and are prone to cervical lymph node metastasis and distant metastasis.<sup>2,6</sup>

In this study, using data from the Head and Neck Cancer Registry of Japan of the Japan Society for Head and Neck Cancer, we examined LEC incidence in the head and neck region in Japan (**Table 1**). Between 2011 and 2019, 84,669 cases of head and neck cancer were reported, including 375 LECs (0.44%). The most common site was the nasopharynx (273 cases), followed by the salivary glands, oropharynx, and laryngopharynx. Laryngeal LECs accounted for 6 of 375 cases. Of 16,532 cases of laryngeal cancer reported from 2011 to 2019, 0.036% were LECs, all occurring in the supraglottis.<sup>3</sup>

Histologically, LECs resemble nonkeratinizing undifferentiated NPCs.<sup>1</sup> In the present case, tumor cells were negative



**Fig. 7** Pathological findings of the permanent specimen preparation ( $\times 200$ ). (A) The tumor cells were EBER-positive. (B) The tumor cells were p16-positive.

**Table 1** Incidence rates of lymphoepithelial carcinomas occurring in different sites of the head and neck region between 2011 and 2019

Site	Number of cases	%
Nasopharynx	273	72.80
Posterior wall	129	
Posterosuperior wall	115	
Other	29	
Major salivary glands	34	9.07
Parotid gland	26	
Submandibular gland	5	
Sublingual gland	2	
Other	1	
Oropharynx	31	8.27
Posterior wall	26	
Anterior wall	4	
Superior wall	1	
Laryngopharynx	20	5.33
Pyriform sinus	13	
Postcricoid region	5	
Posterior wall	1	
Other	1	
Larynx	6	1.60
Supraglottis	6	
Oral cavity	4	1.07
Retromolar region	1	
Buccal mucosa	1	
Inferior gingiva	1	
Floor of mouth	1	
Maxillary sinus	3	0.80
Nasal cavity	1	0.27
Total	375	

Source: Japan Society for Head and Neck Cancer.<sup>3</sup>

for neuroendocrine markers, including chromogranin A, synaptophysin, and INSM1. Positive staining was observed for epithelial markers, including AE1/AE3, p40, p63, and CK5/6, suggesting epithelial origin. Lymphocytic and stromal infiltration, characteristic of LECs, was also observed. Collectively, these findings support an LEC diagnosis.

Although nasopharyngeal LECs are associated with EBV infection, non-nasopharyngeal LECs have been reported both with and without EBV.<sup>2,7</sup> Additionally, some cases have shown HPV infection or p53 mutations, and their associations with non-nasopharyngeal LECs are under investigation.<sup>2,8</sup>

Associations of EBV with head and neck malignancies, such as Burkitt lymphoma, NPC, and nasal NK/T cell lymphoma, have been established. EBV-associated nasopharyngeal cancer is highly metastatic but has a more favorable prognosis than nonvirus-associated cancer.<sup>9</sup>

Regarding the prevalence of EBV infection in cases of non-nasopharyngeal LECs, a systematic review of LECs of the larynx and laryngopharynx by Petruzzi et al reported that 23 of 41 cases were EBV-negative.<sup>10</sup> Petruzzi et al also reported that EBV positivity is a predictor of poor prognosis in non-nasopharyngeal LECs, whereas typical EBV-positive virus-associated cancers in the nasopharynx, including LECs, are prognostically favorable.<sup>10</sup> Nevertheless, relationships between prognosis and EBV infection status in head and neck LECs, including nasopharyngeal and non-nasopharyngeal LECs, remain unknown.

Non-nasopharyngeal LECs are often detected at Stage III or higher, with a cervical lymph node metastasis rate of 70.2%.<sup>7</sup> The estimated 5-year survival rates range from 60 to 70%.<sup>2,8</sup>

No standard treatment procedures have been established because of the paucity of reports on non-nasopharyngeal LECs. Nonetheless, LECs are highly sensitive to radiation, and reported treatment strategies mostly include surgery alone or surgery combined with radiotherapy.<sup>2</sup> In a study of 1,025 patients with LECs of the oral cavity and pharynx, Bai et al reported median overall survival durations of 255 and 190 months in the surgery and nonsurgery groups, respectively, showing that surgery significantly prolonged survival ( $p < 0.01$ ).<sup>8</sup> They also conducted a multivariate Cox proportional hazards analysis and obtained hazard ratios of 0.65 (95% confidence interval [CI]: 0.37–0.99,  $p = 0.04$ ) and 0.76 (95% CI: 0.41–0.92,  $p = 0.03$ ) for surgery and radiotherapy, respectively, reporting both as predictors of favorable prognosis.<sup>8</sup>

A total of eight cases of LECs involving the pharynx and larynx, including the present case and those from previous reports, are summarized in ►Table 2.<sup>2,10–14</sup> Among the cases in which surgery was the first-line treatment, total laryngectomy was performed in Case 3 and total pharyngolaryngectomy, bilateral neck dissection, and free flap reconstruction were performed in Cases 1 and 4. In Case 7, CO<sub>2</sub> laser surgery was performed for tumor removal. Postoperative adjuvant radiotherapy was administered at doses of 54 to 66 Gy. Among the cases in which chemotherapy was selected as the first-line treatment, the EXTREME regimen (cisplatin, cetuximab, and fluorouracil) was administered in Case 5. In Case 2, the patient underwent neoadjuvant chemotherapy with cisplatin and doxorubicin before total pharyngolaryngectomy and bilateral neck dissection. Surgery was chosen as either a first-line or additional treatment in six cases, except for Case 6, which was staged as cT1. Therefore, surgery appears recommendable for locally advanced carcinomas. Chemotherapy also tended to be used as a first-line or additional treatment for N3 or higher stage carcinomas.

In the present case, we planned to treat an EBV-positive laryngeal LEC of cT4aN2aM0 with pharyngolaryngoesophagectomy, bilateral neck dissection, and free jejunal autograft reconstruction, following the treatment strategy for conventional head and neck cancer. During the preoperative waiting period, the patient received two courses of PCE therapy and additional doses of cetuximab as neoadjuvant chemotherapy to prevent tumor progression. Although the efficacy of

**Table 2** Reported cases of non-nasopharyngeal lymphoepithelial carcinomas, including our case

Case number	Author	Primary site	Preoperative diagnosis	Staging	EBV	First-line treatment	Postoperative diagnosis	Additional treatment	Follow-up period	Recurrence	Year reported
1	Faisal et al <sup>2</sup>	Laryngopharynx	cT4N3M0	IVB	+	Surgery	pT4aN3bM0	Adjuvant chemoradiotherapy			2005
2	Kermani et al <sup>10</sup>	Larynx	cT3N1M0	III	+	Induction chemotherapy, surgery	No data	Postoperative radiotherapy	18 mo	-	2015
3	Monteiro et al <sup>11</sup>	Larynx	cT2N2bM0	IVA	+	Surgery	pT2N3bM0	Postoperative adjuvant chemoradiotherapy	9 mo	-	2019
4	Yap et al <sup>12</sup>	Larynx	cT3N2cM0	IVA	-	Surgery	pT3N2cM0	Postoperative radiotherapy	24 mo	-	2021
5	Petruzzi et al <sup>9</sup>	Larynx	cT3N3bM1	IVC	-	Chemotherapy		Surgery, adjuvant chemotherapy	13 mo	-	2022
6	Petruzzi et al <sup>9</sup>	Laryngopharynx	cT1N3bM0	IVB	-	Chemoradiotherapy			9 mo	-	2022
7	Nogal et al <sup>13</sup>	Larynx	no data	No data	No data	Surgery	No data	Postoperative radiotherapy	18 mo	-	2022
8	Our case	Larynx	cT4aN2aM0	IVA	+	Induction chemotherapy, surgery	pT3N2aM0		12 mo	-	2025

Abbreviation: EBV, Epstein-Barr virus.

chemotherapy for LECs has not been established,<sup>2,7</sup> we anticipated that regimens commonly used for NPCs would be effective for LECs because of their histological similarities. In this case, the tumor size was reduced following PCE therapy. However, the usefulness of tyrosine kinase inhibitors and anti-HER2 antibodies is limited, as epidermal growth factor receptor mutations and HER2 expression are infrequently observed in LECs.<sup>8</sup> Among the agents used in PCE therapy, cetuximab was presumably ineffective. The postoperative diagnosis was laryngeal LEC, pT3N2aM0. The patient is being followed up without postoperative adjuvant therapy, as the lymph node metastasis showed no extranodal invasion.

## Conclusion

Non-nasopharyngeal LEC is extremely rare, and early therapeutic intervention is crucial due to its high rates of cervical lymph node and distant metastases as well as its marked tendency for tissue infiltration. Although virus-related carcinomas generally have a favorable prognosis, non-nasopharyngeal LECs should be treated using the strategy for conventional squamous cell carcinomas in the head and neck region, regardless of viral infection status, as the relationship between prognosis and viral infection in these cases remains unclear.

## Conflict of Interest

None declared.

## References

- Barnes L, Eveson JW, Reichart P, et al. Pathology and genetics of head and neck tumours. In: Biernat W, ed. Pathology and Genetics of Head and Neck Tumours. France: IARC Press; 2005:64–69
- Faisal M, Hartenbach S, Schratte A, et al. Lymphoepithelial carcinoma of larynx and hypopharynx: a rare clinicopathological entity. *Cancers (Basel)* 2020;12(09):2431
- Japan Society for Head and Neck Cancer. Report of Head and Neck Cancer Registry of Japan. Accessed October 19, 2023 at: <http://www.jshnc.umin.ne.jp/report.html>
- Arai A, Mitsuda J, Yoshimura K, et al. Limited resection for oral tongue cancer after PCE chemotherapy. *Jpn Soc Head Neck Surg* 2021;31:13–17
- Ose N, Kawagishi S, Funaki S, et al. Thymic lymphoepithelial carcinoma associated with Epstein-Barr virus: experience and literature review. *Cancers (Basel)* 2021;13(19):4794
- Mariotti G, Mariuzzi L, Gaio E, Portaleone S, Pertoldi B, Staffieri A. Lymphoepithelial carcinoma of the larynx. *Acta Otolaryngol* 2002;122(04):429–434
- Galletti C, Pizzimenti C, Cavallari V, Galletti B. Larynx lymphoepithelial carcinoma: surgical management. *BMJ Case Rep* 2021;14(07):e241460
- Bai J, Zhao F, Zhang W, Zheng P, Pan S. Lymphoepithelial carcinoma of the oral cavity and pharynx: a SEER population-based cohort study. *Am J Transl Res* 2023;15(04):2716–2726
- Yoshizaki T. Nasopharyngeal carcinoma and Epstein-Barr virus: carcinogenesis and clinical aspect. *Stomato-pharyngology* 2018; 31:183–186
- Petruzzi G, Costantino A, De Virgilio A, et al. Lymphoepithelial carcinoma of larynx and hypopharynx: a systematic review and pooled analysis. *Eur Arch Otorhinolaryngol* 2022;279(03): 1157–1166

- 11 Kermani W, Belcadhi M, Sriha B, Abdelkéfi M. Epstein-Barr virus-associated lymphoepithelial carcinoma of the larynx. *Eur Ann Otorhinolaryngol Head Neck Dis* 2015;132(04):231–233
- 12 Monteiro F, Baldaia H, Ribeiro L, et al. Epstein-Barr virus-associated with lymphoepithelial carcinoma: a rare tumor of the larynx. *Clin Med Insights Ear Nose Throat* 2019;12:1179550619865551
- 13 Yap JA, Bundele MM, Lim MY, Goh JPN. Lymphoepithelial carcinoma of the larynx: an extremely rare tumour in a patient of Chinese descent. *BMJ Case Rep* 2021;14(10):e245945
- 14 Nogal P, Staśkiewicz M, Jackowska J, Wierzbicka M. Lymphoepithelial carcinoma - a rare tumor of the larynx. Case report. *Front Surg* 2022;9:851481