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ORIGINAL RESEARCH

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# Clinical features in salivary gland lymphoepithelial carcinoma in 10 patients: Case series and literature review

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## Abstract

**Objective:** Lymphoepithelial carcinoma (LEC) accounts for 0.4% of malignant tumors of the salivary gland and 0.8% of parotid gland malignancies. Over the past 50 years, less than 300 cases have been reported in the literature. The purpose of this study was to investigate the characteristics of salivary gland LEC.

**Methods:** We retrospectively reviewed the medical records and analyzed clinical data obtained from 10 patients seen at our hospital between 2005 and 2020 with salivary gland LEC.

**Results:** All patients presented with a self-palpable, non-tender, hard swelling, or lump near the jaw or infra-auricular region. Most cases ($n = 8$) were of solitary tumors, and enhancing patterns on computed tomography mainly were homogenous ($n = 8$). Interestingly, eight patients tested positive for the Epstein–Barr encoding region in in situ hybridization. Still, only three patients had detectable circulating Epstein–Barr virus (EBV) DNA, and one patient had detectable EBV IgA. All patients underwent complete tumor resection, followed by radiotherapy, and six also underwent chemotherapy. Nine patients became disease-free within 5 years, and one died due to disease 4 years after surgery.

**Conclusion:** Although rare and considered to be a high-risk malignancy, LECs have favorable treatment outcomes. Circulating EBV DNA is still not considered a marker for preoperative assessment or postoperative treatment response. The role of EBV DNA requires further investigation.

Level of Evidence: 4

KEYWORDS

Epstein–Barr virus, lymphoepithelial carcinoma, parotid tumor, salivary gland neoplasm

## 1 | INTRODUCTION

Salivary gland malignancies are uncommon, and lymphoepithelial carcinoma (LEC) accounts for 0.4% of malignant tumors of the salivary gland and 0.8% of parotid gland malignancies.[1,2] They are known to occur in Taiwanese, southern Chinese, Mongolian, Inuit and Aleut, and African populations.[1,3] Few studies have focused on the demographic characteristics and imaging findings of these patients and appropriate treatment modalities in comparison with other parotid tumors. Over the past 50 years, less than 300 cases have been

reported in the literature.[3] The lack of attention is significant because understanding the clinical manifestations of these patients will provide benefits in further treatment plans. To better understand this rare salivary gland malignancy, we retrospectively analyzed the preoperative clinical manifestations, imaging findings, laboratory data, and follow-up treatment outcomes of 10 patients and analyzed the factors that influenced the prognosis.

## 2 | PARTICIPANTS AND METHODS

Clinical data were retrospectively collected from 2005 to 2020 in the Department of Otolaryngology of the National Cheng Kung University Hospital in Taiwan. A total of 10 patients were recruited. The average age (SD) was 42.9 (14.7) years (range = 12–58 years). The follow-up lasted for 4–192 months. The demographic data, disease history, image findings, cancer status, and combination of concurrent chemoradiotherapy (CRT) or radiotherapy (RT) only are presented in Table 1. This study was conducted in accordance with the guidelines of the Declaration of Helsinki and was approved by the Institutional Review Board of National Cheng Kung University Hospital, Tainan, Taiwan (B-ER-110-354).

## 3 | RESULTS

### 3.1 | Clinical manifestations

A total of 10 patients were enrolled in this study; most had parotid tumors ($n = 8$) and the rest had tumors in the submandibular gland ($n = 2$). Males ($n = 5$) and females ($n = 5$) were equally affected. The initial presentation of the patients was a self-palpable, non-tender, hard swelling or lump near the jaw or infra-auricular region. The duration of symptoms varied from months to years.

### 3.2 | Computed tomography findings

Based on our experience, most LEC lesions are well defined with regular margins. The largest axis of the tumor upon diagnosis was around

**TABLE 1** Demographic information of the 10 patients.

| Case No. | Age/Sex | Location | Circulating EBV DNA | EBER | TNM stage | RT | CT | Status | F/U (mos) |
|---|---|---|---|---|---|---|---|---|---|
| 1 | 53F | parotid | NA | NA | IVa | + | – | Alive, NED | 192 |
| 2 | 48 M | parotid | + | + | IVa | + | + | ALIVE, NED | 163 |
| 3 | 51F | parotid | – | + | II | + | – | Alive, NED | 120 |
| 4 | 44 M | parotid | NA | + | II | + | – | alive, NED | 54 |
| 5 | 47F | parotid | + | + | IVa | + | + | Dead, Disseminated disease | 40 |
| 6 | 58 M | parotid | – | – | IVa | + | + | Alive, NED | 74 |
| 7 | 31 M | parotid | – | + | IVa | + | + | Alive, NED | 8 |
| 8 | 58F | SMG | + | + | III | + | + | Alive, NED | 76 |
| 9 | 12 M | SMG | – | + | IVa | + | + | Alive, NED | 140 |
| 10 | 27F | parotid | – | + | II | + | – | Alive, NED | 4 |

Abbreviations: CT, chemotherapy; EBER, Epstein–Barr encoding region; EBV, Epstein–Barr virus; F/U, follow-up; mos, months; NA, not applicable; NED, no evidence of disease; RT, radiotherapy; SMG, submandibular gland.

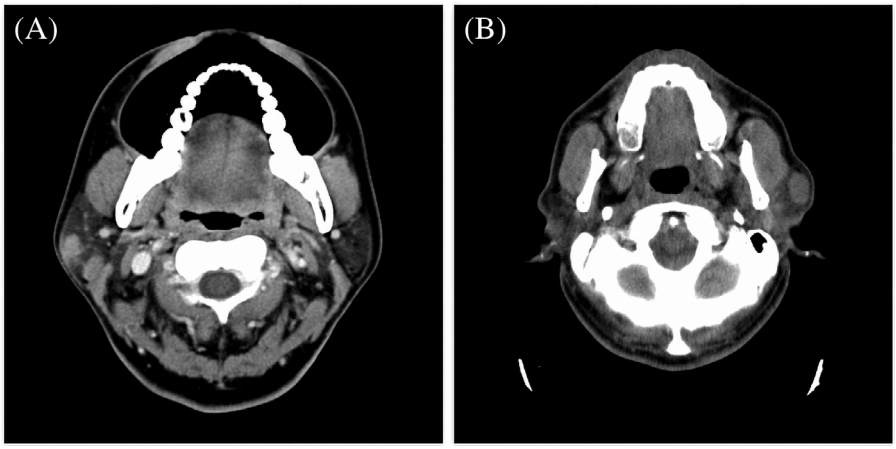


**FIGURE 1** Computed tomography findings. Most lymphoepithelial carcinoma lesions are solitary with a homogenous enhancing pattern.

**TABLE 2** Imaging characteristics of the patients.

| Case No. | Tumor size (cm) | Lesion | Margin | Enhancement pattern | Cystic degeneration | Density[a] | U/S |
|---|---|---|---|---|---|---|---|
| 1 | 2.3 × 1.4 | Diffuse | Irregular | Heterogenous | + | Hypo | NA |
| 2 | 1.6 × 1.2 | Solitary | Regular | Homogenous | − | Iso-to- hyper | NA |
| 3 | 2.0 × 1.2 | Solitary | Regular | Homogenous | − | Hyper | Cystic mass with septa |
| 4 | 3.0 × 1.8 | Solitary, Lobulated | Regular | Homogenous | − | Hyper | NA |
| 5 | 2.0 × 1.5 | Multiple | Regular | Homogenous | + | Hyper | NA |
| 6 | 3.2 × 2.2 | Solitary | Regular | Heterogenous | − | Iso-to-hyper | NA |
| 7 | 2.4 × 1.7 | Solitary | Regular | Homogenous | − | Hyper | NA |
| 8 | 2.3 × 1.7 | Solitary | Regular | Homogenous | + | Hypo | Hypoechoic mass |
| 9 | 3.0 × 2.7 | Solitary | Irregular | Homogenous | − | Iso-to-hypo | NA |
| 10 | 2.5 × 1.8 | Solitary | Regular | Homogenous | − | Hyper | Hypoechoic mass |

Abbreviations: NA, not applicable; U/S, ultrasound.
[a]Density compared to the surrounding salivary glands.

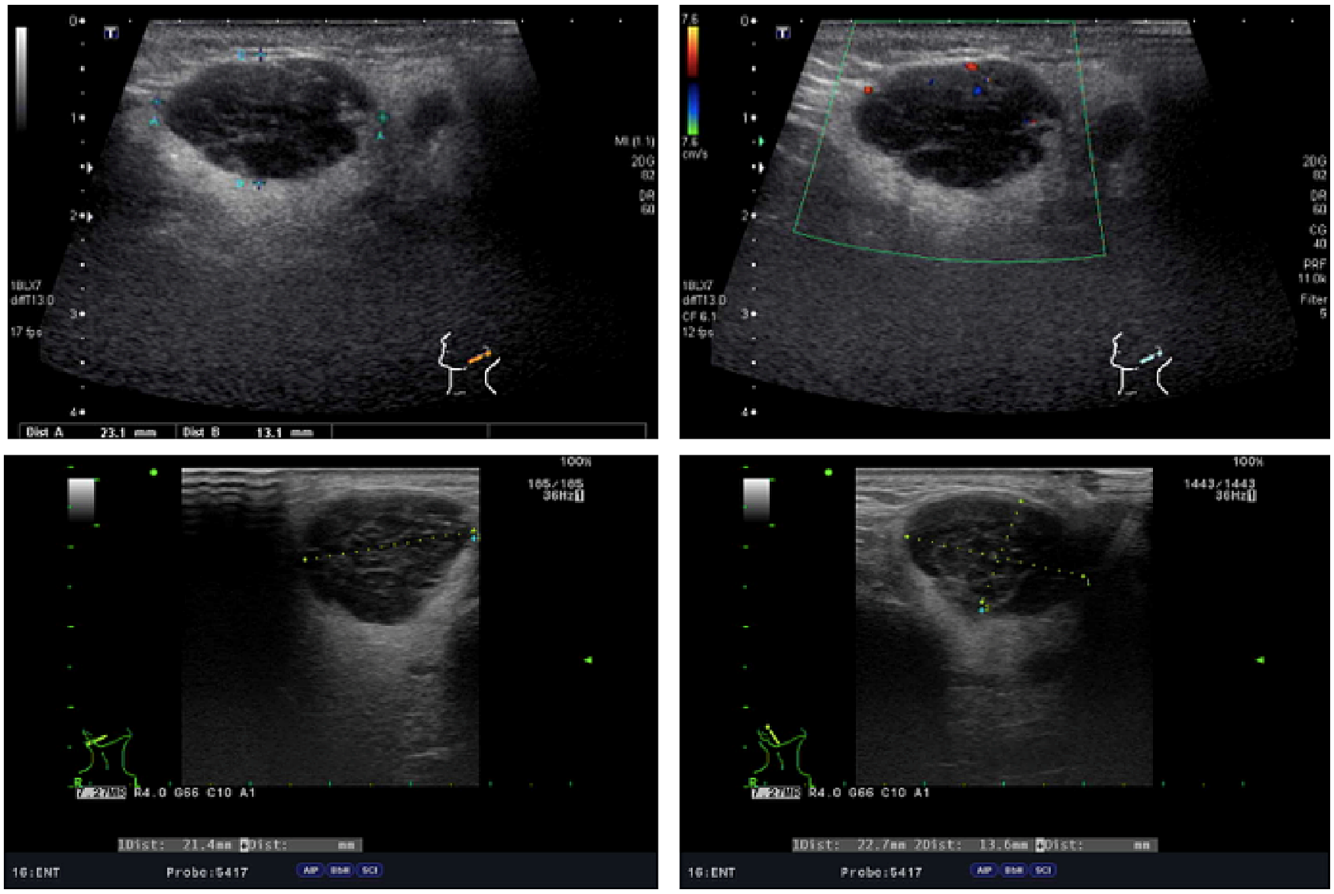

**FIGURE 2** Ultrasonography findings. Two cases with ultrasonographic examinations showed that the lymphoepithelial carcinoma lesions are hypoechoic with a sharp margin and heterogenous content.

2.0–3.2 cm. Most of the LEC lesions were solitary ($n = 8$); however, multiple lesions were noted in some cases ($n = 2$). The enhancing patterns were mostly homogenous ($n = 8$). The density compared to the surrounding salivary glands was isodense to slightly hyperdense (Figure 1) and was sometimes complicated with cystic degeneration ($n = 3$) (Table 2).

### 3.3 | Ultrasonography findings

Three cases with ultrasonographic examinations showed that the LECs were mostly hypoechoic with a sharp margin and heterogeneous content (Figure 2). Only one case in our series received fine-needle aspiration (case no. 10), which found cytologic atypia.

### 3.4 | Pathology

According to our cases, the tumors consist of cords, sheets, and islands of undifferentiated epithelial cells, which are separated by a lymphoid-rich stroma. Tumor cells show eosinophilic cytoplasm, vesicular nuclei, and conspicuous nucleoli with indistinct cell borders. The lymphoid-rich stroma is composed of small lymphocytes and plasma cells, with germinal center formation. Mitotic activity and apoptotic bodies are evident. Epstein–Barr encoding region in situ hybridization (ISH) was positive in 8 out of 10 patients tested (Table 1).

### 3.5 | Laboratory findings

Eight of the 10 cases received laboratory examinations, including Epstein–Barr virus (EBV) IgA, and DNA titer. Circulating EBV DNA was detected in three patients. One patient had detectable EBV IgA levels.

### 3.6 | Treatment and outcome

All patients underwent surgery for complete tumor resection, followed by RT. Six cases diagnosed at an advanced stage due to nodal metastasis received chemotherapy (case no. 2, 5–9). We used a single-agent regimen for chemotherapy: weekly cisplatin, 30–40 mg/m$^2$ in normal saline, 250 cc infused for 2 h. A total of 4–8 cycles were given.[4] Although case no. 1 had stage IVa disease, the patient had advanced T stage with adequate surgical margins and N0 status and was therefore treated with RT alone without chemotherapy.

Nine patients achieved disease-free status during the follow-up period, except for one patient who died due to disease 4 years after surgery. The overall 1-, 3-, and 5-year survival rates were 100%, 100%, and 85.7%, respectively.

## 4 | DISCUSSION

Salivary gland cancers are relatively rare, accounting for 1%–6% of all neoplasms of the head and neck. Malignant lesions are found in approximately 20% of all salivary gland neoplasms.[5] LEC is an uncommon malignancy of salivary glands, accounting for approximately 0.4% of malignant tumors of the salivary glands.[1] According to a previous retrospective study from our institute, LEC accounts for only 0.8% of parotid tumors.[2] The most common location of LECs is the nasopharynx, and all cases are associated with EBV infection. Therefore, when LEC is found outside the nasopharynx, it is important to determine if there is a primary tumor elsewhere. Additionally, lymphoepithelial lesions are reported to be a tissue manifestation of autoimmune diseases, such as primary or secondary Sjögren's syndrome.[6] Leung et al. reported 10 cases of LEC, none of which had a history of Sjögren's syndrome.[7] None of our patients had concomitant Sjögren's syndrome.

In this report, LEC in the salivary glands predominantly occurred in the parotid glands rather than in the submandibular glands. Both sexes were equally affected. The average age at diagnosis is 40–50 years. These results are similar to Whaley et al. reported in 2020.[8] According to the clinical manifestations and imaging findings of LEC, it is difficult to make a differential diagnosis of salivary gland mass based on preoperative findings. Computed tomography may be helpful in distinguishing malignant from benign lesions. Ban et al.[9] reported the morphologic patterns of 28 LECs. They were categorized into three types according to the margin and shape of the lesions: type 1 masses were round or ovoid with a well-defined margin, type 2 masses showed a lobulated or plaque-like shape with a partially or ill-defined margin, and type 3 masses showed an irregular shape with an ill-defined margin and diffuse invasive growth. As is already widely known, irregular or poorly defined margins suggest a malignant tumor. However, in our cases, only 2 out of 10 patients in this report had poorly defined margins and irregular borders. Still, there are some hints suggestive of LEC, such as homogenous, solitary, and iso- to hyperdense-enhancing patterns. Even so, these characteristics share a similar pattern with numerous parotid tumors. Therefore, surgical excision by parotidectomy with an adequate margin of normal tissue and to avoid tumor rupture is considered necessary.

The association between EBV and salivary gland LECs has been well described. The prevalence of LECs seems to be higher in EBV-endemic areas.[8,10] In our cohort of patients, the positive rate of EBV ISH among all cases was 80% ($n = 8$). Previous reports showed that in EBV-endemic areas, such as Southeast Asia, Greenland, and Alaska, all LEC cases tested positive for EBV.[3] According to Tsai et al., *EBER1* was detected in malignant epithelial cells in all seven cases of LEC but not in any other carcinomas or in the neighboring normal salivary gland tissue.[11]

Additionally, we found that four out of eight patients with positive EBV ISH had no detectable circulating EBV DNA. Consequently, the use of serum EBV DNA as a marker for preoperative assessment remains questionable. As for predicting treatment response, the presence of free circulating EBV DNA in the serum has already been established for nasopharyngeal cancer and LEC of the stomach and lung,[12] suggesting the feasibility of monitoring response to therapy in advanced cases.

The treatment of choice for most salivary gland neoplasms is complete surgical excision by parotidectomy. In terms of the necessity of neck dissection, according to our series, the percentage of cervical lymph node involvement at the time of presentation was 60%, with similar results reported by Whaley et al. (43%).[8] Both were higher than other previous reports (around 15%).[9,13,14] Some studies reported that routine elective neck dissection of levels I, II, and III in

all patients with primary carcinoma of the parotid gland provides a favorable outcome.[15] However, to date, the elective treatment of a clinical N0 neck remains controversial. For patients with clinically positive cervical lymph nodes, therapeutic neck dissection is still strongly recommended at the time of primary surgery, followed by adjuvant RT, regardless of histology or site.[16] Postoperative RT can be used as an adjuvant therapy in patients with high-risk factors, such as close or invaded margins, perineural speed, lymphatic and/or vascular invasion, lymph node involvement, and high-grade histology.[17] Recent studies indicated that postoperative CRT showed a trend toward higher locoregional control rates than those treated with RT alone. However, adjuvant CRT appears to have a higher risk of drug toxicity and increased mortality; therefore, overall survival for CRT versus RT alone was significantly inferior.[18] Chemotherapy is a palliative treatment applied to patients experiencing symptomatic locally recurrent and/or metastatic disease that is not amenable to further surgery or radiation.[16]

At the end of our follow-up period, the survival time ranged from 4 to 192 months. The median follow-up period was 75 months. There were nine surviving patients, and one died of LEC. The initial stage of mortality was pT1N2M0 stage IVA. The patient died of distant failure 40 months after the initial surgery. Overall, we shared similar prognostic results with those of Hsiung et al., who reported distant failure in two out of nine patients with LEC.[19] According to a previous study, patients with LECs of salivary glands were shown to have favorable prognoses with a low rate of local or regional failure. However, LECs are still categorized as high-risk salivary gland cancers and have a tendency to spread to cervical lymph node metastasis.[8] Additionally, there are no clinicopathological or therapeutic features suitable as predictive factors for prognosis.[20] Therefore, for patients with advanced N stage, the risk of distant metastasis should be carefully monitored.

## 5 | CONCLUSION

Although rare and considered to be a high-risk malignancy, LECs have favorable treatment outcomes. Meticulous preoperative assessments, including the status of neck metastasis, were significant. Circulating EBV DNA is still not considered a marker for preoperative assessment or postoperative treatment response. The role of EBV DNA requires further investigation.

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### CONFLICT OF INTEREST

The authors have no conflicts of interest to disclose.

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