**ORIGINAL PAPER**

# Lymphoepithelial Carcinoma of Salivary Gland EBV-association in Endemic versus Non-Endemic Patients: A Report of 16 Cases

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## Abstract

Lymphoepithelial carcinoma of salivary glands (LECSG) are rare neoplasms, reported in endemic populations (southeastern Chinese) with a strong Epstein-Barr virus (EBV) association. A retrospective series comparing EBV status within an ethnically diverse population (endemic vs. non-endemic patients) has not been reported. Sixteen LECSG were equally distributed between males (n = 8) and females (n = 8) with a median age of 54 years (range 18 to 85 years) at initial diagnosis. Ten patients were white, 4 Asian, and 2 black. The patients typically presented with swelling or mass for an average of 11.6 months. Tumors affected only major salivary glands: parotid (n = 13); submandibular (n = 3). Tumors were an average of 2.9 cm (range 1.5 to 5.8 cm). Nine of 16 (56%) patients had cervical lymph node metastases at presentation. No patients had nasopharyngeal or oropharyngeal tumors. Microscopically, the tumors were widely infiltrative, characterized by large polygonal to spindled cells arranged in a syncytial, lattice-like network in a background of lymphoplasmacytic cells. The neoplastic cells showed an open-vesicular nuclear chromatin to a more basaloid-morphology, the latter showing hyperchromatic nuclei and less cytoplasm, while nearly all of the cases had associated lymphoepithelial lesions/sialadenitis. By in situ hybridization, 8 of 16 cases had a strong, diffuse EBER expression (4 of 4 Asians; 4 of 12 non-Asians), while with immunohistochemistry all cases tested were pan-cytokeratin, CK5/6 and p63 reactive; none of the cases tested were p16 reactive. All patients were managed with wide or radical excision, 4 with concurrent chemoradiation, and 6 with radiation alone. Distant metastasis (lung, brain, and bone) developed in 2 patients. Overall follow-up (mean 3.8 years) revealed 12 patients alive and 2 dead, none with evidence of disease (mean 4.3 years); one white male alive with disease at 1.9 years, and one Asian female dead of disease at 4.2 years; both of these latter patients had Group IV stage disease. High stage (Group IV) patients had a shorter mean survival than lower stage patients: 3.1 versus 4.8 years, respectively. In conclusion, LECSG are uncommon primary neoplasms. Concurrent lymphoepithelial lesions may help suggest a primary tumor. The tumors, irrespective of race or ethnicity, may express EBER. There is an overall good survival, perhaps better for EBV-negative patients and for those with lower stage disease.

**Keywords** Lymphoepithelial carcinoma · Salivary glands · Immunohistochemistry · EBER · Ethnic groups

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## Introduction

Lymphoepithelial carcinoma (LEC) is a category of malignancy that encompasses an undifferentiated appearing squamous cell carcinoma that is associated with a prominent, nonneoplastic lymphoplasmacytic cell infiltrate [1]. Morphologically it is indistinguishable from undifferentiated nasopharyngeal carcinoma (NPC), which is the prototypical LEC [2–5]. LEC of salivary glands (LECSG) has been reported to develop with the same high frequency in endemic populations who have the highest incidence of NPC, where nearly all cases are documented to be associated with Epstein-Barr virus (EBV). The

endemic populations include South East Asian and Artic Inuit populations (Greenland, northern Canada, Alaska) [6–15], with LECSG rates of up to 92% of all malignant salivary gland tumors [16]. By contrast, in non-endemic regions (such as the United Kingdom and the United States of America), the tumors represented 0.3 to 0.7% of all malignant salivary gland tumors [17, 18]. Even in the non-endemic regions, whites only represent about 7% of all reported cases, and as such a comment about EBV-association in non-endemic patients has not been well documented. This study was undertaken to report EBV-association in a cohort of patients from the United States of America and Central America (non-endemic regions) who had LECSG.

## Methods

Sixteen cases of salivary gland tumors diagnosed as "lymphoepithelial carcinoma," "anaplastic carcinoma," "malignant lymphoepithelial lesion," "lymphoepithelioma-like carcinoma," and "carcinoma ex lymphoepithelial lesion" were retrospectively selected from the clinical files of the authors between 2008 and 2019. Ten cases were identified within one healthcare delivery system treating more than 4 million patient members. Materials within the files were supplemented by a review of the patient demographics (sex, age, race) and symptoms at presentation (mass, nerve symptoms, hearing changes, ulceration, other findings), including duration. Smoking and alcohol history and any other concurrent findings were identified. In addition, we reviewed the medical history, surgical pathology and operative reports, specifically noting exact tumor location, lateralization, and tumor size (greatest dimension in centimeters). Documentation of evaluation of the nasopharynx and oropharynx was included. Imaging findings, when performed, were reviewed. Follow-up data included information regarding the specific treatment, the presence or absence of recurrent or persistent disease, and the current status of the disease and patient. This clinical investigation was conducted in accordance and compliance with all statutes, directives, and guidelines of an Internal Review Board authorization (#5968) performed under the direction of Southern California Permanente Medical Group relating to human subjects in research.

Hematoxylin and eosin-stained slides from all cases were reviewed. The following specific macroscopic and histologic observations were recorded for each tumor: tumor bosselation or lobulation; presence of salivary gland tissue; capsular invasion; perineural invasion; lymphovascular invasion; lymphoepithelial sialadenitis; mitotic index; pattern of growth; granuloma formation; amyloid deposition; lymph node number and affected lymph node number; and the presence of other microscopic pathologic findings. Staging was defined by American Joint Committee on Cancer (AJCC) Staging Manual 8th edition.

Immunophenotypic analysis was performed in all cases by a standardized Envision™ method employing 4 μm-thick, formalin fixed, paraffin embedded sections. Antibodies included AE1/AE3 (pan-cytokeratin, Dako and Becton-Dickson), CK5/6 (Dako), p63 (Leica Microsystems), p40 (BioCare), 34βE12 (K903 by Sigma), p16 (MTM Laboratories), among others (the unspecified studies were not performed on all cases). Epitope retrieval was performed, as required by the manufacturer guidelines. Standard positive controls were used throughout, with serum used as the negative control. In situ hybridization for Epstein-Barr encoding region (EBER) for small RNAs was performed using an automated benchmark XT system (Ventana Medical Systems, Inc., Tucson, AZ) with the reaction developed using a Hybrid Ready Detection Kit (Ventana Medical Systems, Inc., Tucson, AZ). Positive signals included punctate or diffuse reactivity within tumor nuclei, with RNA controls and negative controls included.

## Results

### Clinical

The clinicopathologic information is summarized in Tables 1 and 2. The patients included 8 females and 8 males who ranged in age from 18 to 85 years, with a mean age at presentation of 55.4 years. There was no difference in mean age at presentation between men and women, but the Asian patients presented at a younger age than the non-Asian patients, although not statistically significant (p = 0.078). There were 2 black, 4 Asian and 10 white patients. All of the patients presented with a mass, and 3 had documented facial nerve weakness and/or nerve paralysis. There were no changes in hearing and no surface ulceration. Other findings included a history of childhood leukemia managed by radiation and chemotherapy; dermatomyositis; atopic dermatitis; and rheumatoid arthritis. Three patients had previous parotid gland tumors: pleomorphic adenoma in two patients, 5 and 8 years previously; and a Warthin tumor 16 years before in the same affected gland. One patient had a history of lung and colon carcinoma. Symptoms were present from 3 to 36 months, with an average of 11.6 months. There was no difference between men and women (p = 0.784) or Asian and non-Asian patients (p = 0.512). Tobacco use was reported in 5 patients and alcohol abuse in 4, but this parameter was not recorded in all patients. All patients had concurrent evaluation of the nasopharynx and oropharynx by endoscopic

**Table 1** Patient Information for Lymphoepithelial Carcinomas of Salivary Gland

| No | Age (years)/sex/race | Site/side/size (cm) | Symptom duration (months) | Unique clinical findings | LESA | pT | pN | AJCC8 Stage Group | EBER | Treatment | Status (years) |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 18 F A | S R 2.6 | 3 | | + | 2 | 1 | 3 | + | WE | Alive, NED, 6.6 |
| 2 | 52 F A | P L 3.3 | 4 | Nerve symptoms; atopic dermatitis; pleomorphic adenoma 8 years previous | + | 4 | 2b | 4 | + | RE | Dead, disseminated disease (lung, brain), 4.2 |
| 3 | 60 F A | P L 3.0 | 3 | Ruptured cyst; Warthin tumor 16 years previous | + | 2 | 2b | 4 | + | RE, Rads, Chemo | Alive, NED, 9.4 |
| 4 | 46 M A | S R 5.8 | 18 | Hypertension | + | 3 | 0 | 3 | + | RE, Rads, Chemo | Alive, NED, 8.0 |
| 5 | 56 F B | P R 2.1 | 3 | Facial weakness | + | 2 | 0 | 2 | − | RE, Rads | Alive, NED, 1.0 |
| 6 | 50 M B | P L 3.2 | 60 | | − | 2 | 0 | 2 | − | WE, Rads | Alive, NED, 0.3 |
| 7 | 50 F W | P L 1.5 | 12 | Dermatomyositis | + | 1 | 0 | 1 | + | WE, Rads | Alive, NED, 1.6 |
| 8 | 53 F W | P L 1.6 | 11 | | + | 1 | 0 | 1 | + | RE | Dead, NED, 6.1 |
| 9 | 60 F W | P L 1.1 | 12 | Facial weakness; fell with facial injury | − | 1 | 2b | 4 | − | WE, Rads | Alive, NED, 2.0 |
| 10 | 77 F W | S L 3.0 | 36 | Skin basal cell carcinomas; pleomorphic adenoma 5 years previous; history of lung and colon carcinomas | + | 2 | 1 | 3 | − | WE | Dead, NED, 4.4 |
| 11 | 42 M W | P L 0.7 | 1 | Childhood leukemia at age 8 treated by radiation and chemotherapy | − | 1 | 0 | 1 | − | WE, Rads | Alive, NED, 6.0 |
| 12 | 54 M W | P R 3.0 | 2 | | + | 2 | 0 | 2 | − | RE | Alive, NED, 4.0 |
| 13 | 54 M W | P R 4.5 | 3 | | + | 3 | 3b | 4 | + | RE, Rads | Alive, NED, 0.6 |
| 14 | 59 M W | P R 4.2 | 7 | | + | 4 | 3b | 4 | + | RE, Rads, chemo | Alive, disseminated disease (bone), 1.9 |
| 15 | 71 M W | P L 2.5 | 3 | | + | 2 | 2b | 4 | − | RE, Rads | Alive, NED, 0.8 |
| 16 | 85 M W | P L 4.0 | 8 | Rheumatoid arthritis | + | 3 | 1 | 3 | − | RE | Alive, NED, 10.2 |

Patients ordered by race, sex and then age. pT, primary tumor category; pN, regional lymph node category; AJCC8, American Joint Committee on Cancer staging manual 8th edition

LESA lymphoepithelial sialadenitis, EBER Epstein-Barr virus encoding region, F female, M male, A Asian, B black, W white, S submandibular, P parotid, L left, WE wide excision, RE radical excision, Rads radiotherapy, chemo chemotherapy, NED no evidence of disease

**Table 2** Aggregated findings of 16 Lymphoepithelial Carcinomas of Salivary Gland (LECSG)

| Characteristics[a] | Number (n = 16) |
|---|---|
| Sex | |
| Female | 8 |
| Male | 8 |
| Age (years) | |
| Range | 18–85 |
| Mean | 55.4 |
| Median | 54.0 |
| *Asian patients (mean)* | 44.0 |
| *White and black patients (mean)* | 59.3 |
| Ethnicity | |
| White | 10 |
| Asian | 4 |
| Black | 2 |
| Symptom duration (months) | |
| Range | 3–36 |
| Mean | 11.6 |
| Clinical presentation | |
| Parotid mass | 13 (81%) |
| Submandibular mass | 3 (19%) |
| Lymph node involvement at presentation | 9 (56%) |
| Laterality | |
| Left | 10 |
| Right | 6 |
| Tumor size (cm) | |
| Range | 1.5–5.8 |
| Mean | 2.9 |
| *Females (mean)* | 2.3 |
| *Males (mean)* | 3.5 |
| *Asians (mean)* | 3.7 |
| *Non-Asians (mean)* | 2.6 |
| EBV status | |
| EBER positive (4 of 4 Asians; 4 Whites) | 8 |
| EBER negative | 8 |
| Group stage (AJCC8) | |
| I (NED, 4.5 years) | 3 |
| II (NED, 1.8 years) | 3 |
| III (NED, 7.3 years) | 4 |
| IV (2 with disease, 3.0 years; 4 NED, 3.2 years) | 6 |
| Therapy | |
| Surgery only (average follow-up: 5.9 years) | 6 |
| Surgery and radiation (average follow-up: 1.8 years) | 6 |
| Chemoradiation (average follow-up: 5.2 years) | 4 |
| Patients with follow up (n = 16) (mean years of follow-up) | |
| No evidence of disease | 14 (4.3) |
| Alive with disease | 1 (1.9) |
| Died of disease | 1 (4.2) |
| Follow up (years) | |
| Range | 0.3–10.2 |
| Mean | 4.2 |
| Follow up (years) | |
| Submandibular gland primaries (n = 3) | NED, 6.3 |

**Table 2** (continued)

| Characteristics[a] | Number (n = 16) |
|---|---|
| Parotid gland primaries (n = 13) | 2 with disease, 3.0 years; 11 NED, 3.8 years |
| EBER positive (n = 8) | 2 with disease, 3.0 years; 6 NED, 5.4 years |
| EBER negative (n = 8) | NED, 3.6 |

[a]Not stated in all cases; AJCC8, American Joint Committee on Cancer staging manual 8th edition

evaluation and/or imaging, without tumor documented in these sites. All tumors developed in major salivary glands, with 13 in the parotid gland and 3 in the submandibular gland. Imaging studies (documented in 13 patients as computed tomography, magnetic resonance imaging and/or ultrasound) demonstrated a solid to multilobular cystic mass within the salivary gland parenchyma, often showing heterogenous mixed enhancement, while also documenting lymph node involvement of the cervical lymph node chains (Fig. 1a).

## Pathologic Features

### Macroscopic

The tumors ranged in size from 1.5 up to 5.8 cm, with a mean of 2.9 cm. Tumors in female patients were smaller than in male patients (p = 0.067), and smaller in non-Asians than in Asian patients (p = 0.162), but these findings were not significant. On gross examination, the tumors were unencapsulated, showing a lobular, firm, tan-white cut appearance, infiltrative into the adjacent parenchyma (Fig. 1b).

### Microscopic

The tumors were infiltrative into the adjacent salivary gland tissue (Fig. 2a, b) and soft tissues (Fig. 2c). Perineural invasion was noted in several cases (Fig. 2d). Background lymphoepithelial sialadenitis (LESA) was noted in the majority of cases (n = 13; Fig. 3a), while granulomatous inflammation was also noted (n = 3; Fig. 3b). The tumor cells were arranged as isolated undifferentiated neoplastic cells with an intimate relationship to the lymphoid elements (Fig. 4a), or more in sheets, cords and nests or islands of syncytial neoplastic cells



**Fig. 1 a** A left parotid gland well defined hyperintense mass (arrow) on T2 weighted coronal MR, fat suppressed image. **b** There is a fish-flesh pale cut surface to a mass replacing much of the parotid gland
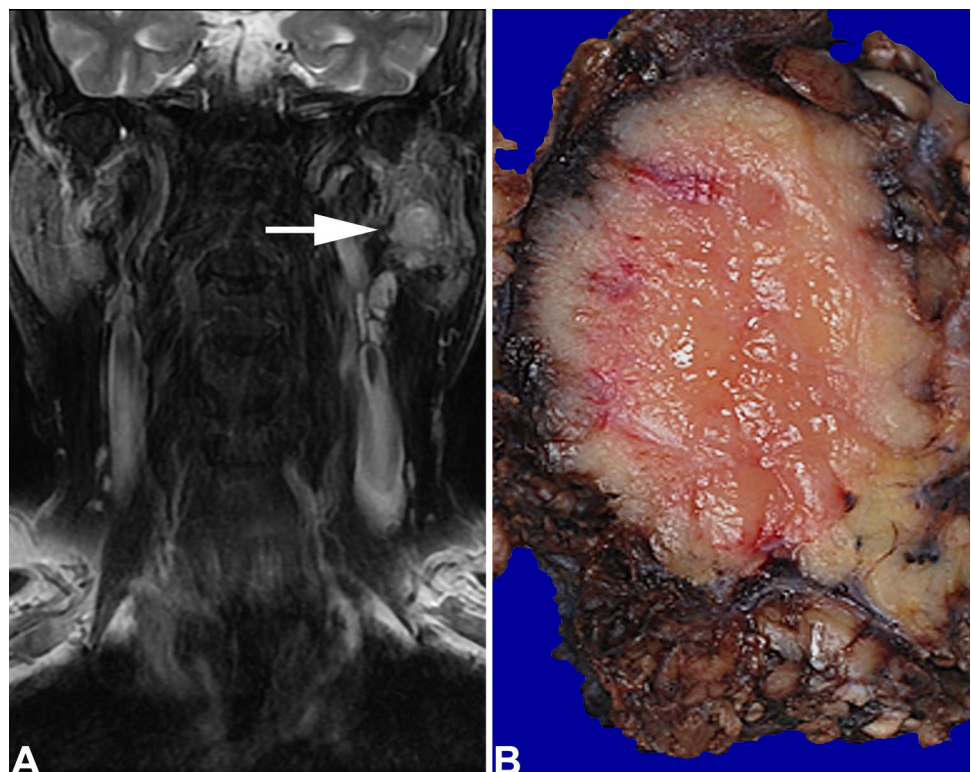
**Fig. 2** **a** Broad sheets and nests of neoplastic cells invade into the parotid gland as large islands (10x). **b** Smaller islands of epithelial cells associated with sclerosis and tumor necrosis (20x). **c** Infiltration of the neoplastic cells into the adjacent adipose tissue (100x). **d** Perineural invasion by the neoplastic cells (400x)
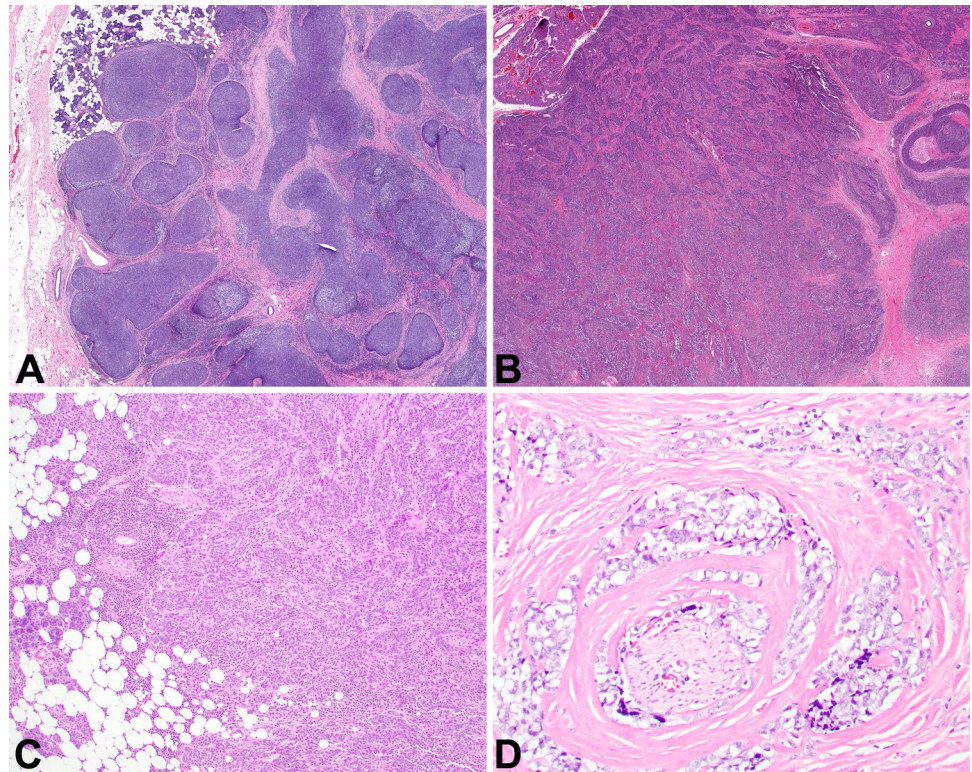


**Fig. 3** **a** Squamous metaplasia of a duct, with an associated lymphoepithelial lesion showing an intimate relationship between the lymphoid elements and the epithelium, but without atypia (400x). **b** Numerous foreign-body type giant cells are seen at the advancing edge of the tumor, representing a granulomatous reaction (400x)
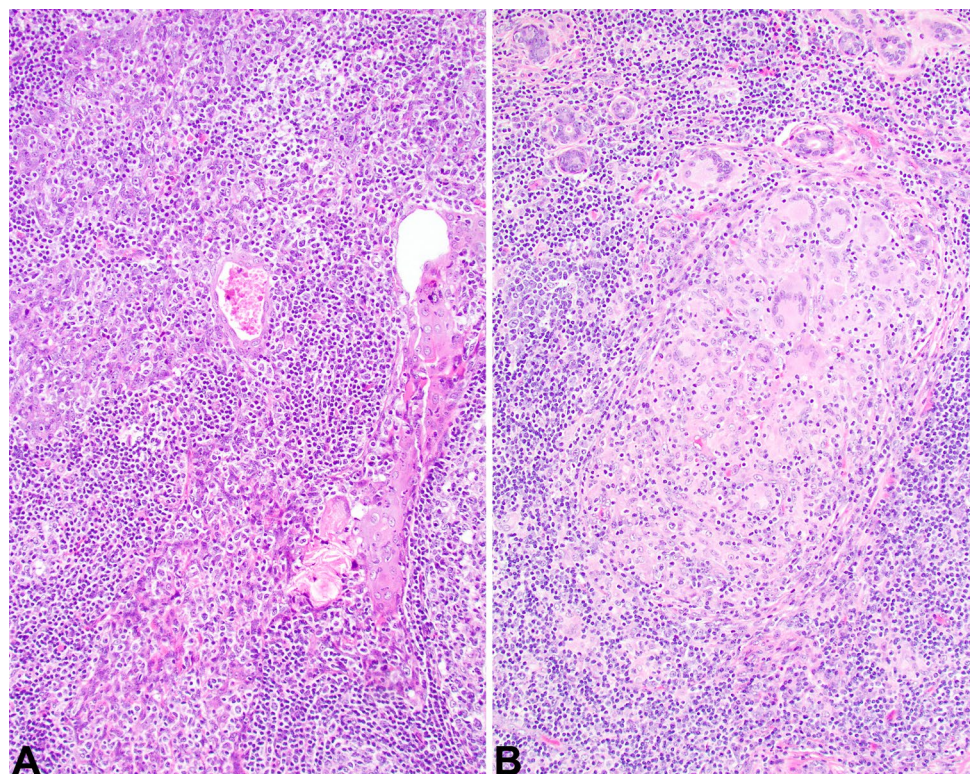
**Fig. 4** **a** The neoplastic cells are difficult to identify as they blend with the lymphoid stroma (400x). **b** Islands of interconnecting neoplastic cells (200x). **c** A sheet-like distribution of syncytial neoplastic cells (400x). **d** A jigsaw puzzle-like architecture with prominent sclerotic stroma (100x)
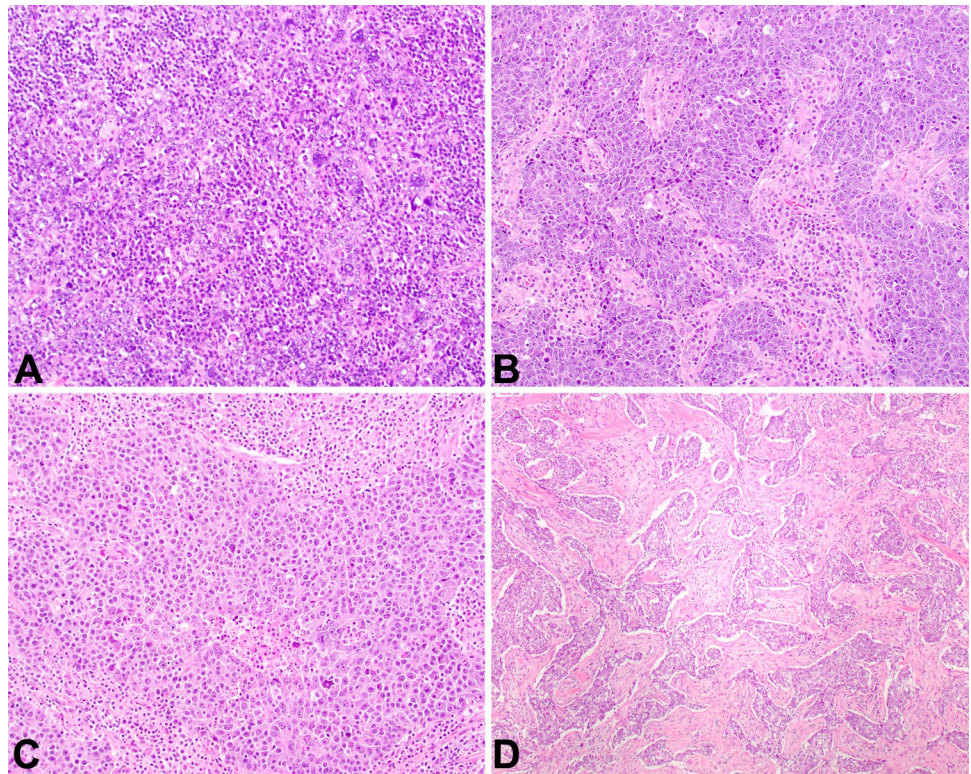


surrounded by the lymphoid stroma (Fig. 4b, c). A jigsaw puzzle appearance was noted, but was not the dominant finding (Fig. 4d). Mitotic activity was greatly increased and included atypical forms. The neoplastic cells were crowded, large, undifferentiated cells with a very high nuclear to cytoplasmic ratio. Their nuclei were irregular to oval with open to vesicular nuclear chromatin with prominent, hypereosinophilic nucleoli (Fig. 5a), while in more basaloid areas, the nuclei were more hyperchromatic. Isolated areas of keratinization were seen in a few cases (Fig. 5b). Pleomorphism was conspicuous (Fig. 5c). Tumor cell spindling was noted in several cases (Fig. 5d). The cytoplasm was sparse, delicate, eosinophilic to amphophilic with indistinct cell borders.

### Immunohistochemical and In Situ Hybridization Results

All tumors tested demonstrated a squamous epithelial phenotype, with reactions to CK5/6 (Fig. 6a), AE1/AE3 (Fig. 6b), p40, p63 (Fig. 6c), EMA and CK903. EBER ISH was positive in 8 of 16 cases tested (Fig. 6d). While these EBV studies confirmed the diagnosis is endemic patients, they were not always seen in non-endemic patients (Table 1). Thus, in this series, 8 of 16 tumors tested lacked EBER and/ or LMP1, a finding seen in 6 white patients and 2 black

patients (Tables 1 and 2). The overall histologic pattern and epithelial reactivity was still characteristic of LECSG in these non-EBV-associated eight patients.

### Treatment and Follow-up

All patients were managed by surgery, including wide excision and total parotidectomy (Table 1). At the time of presentation and initial management, 7 patients (4 EBV-negative) had no lymph node disease. The remaining 9 patients had lymph node involvement: 3 patients with pN1; 4 patients with pN2b; and 2 patients with pN3b disease. Based on the tumor size and extent of invasion, there were 4 pT1, 7 pT2, 3 pT3 and 2 pT4 tumors. Thus, overall, based on the AJCC 8th edition staging, there were 3 Group I; 3 Group II; 4 Group III; and 6 Group IV patients, respectively. Irrespective of treatment, all Group I, II, and III patients were either alive or had died of unrelated causes, and were without evidence of disease at last follow-up (mean follow-up, 4.3 years). In Group IV patients (overall mean, 3.1 years), 2 patients were alive or had died with disease (mean 3.0 years) with the remaining 4 patients alive without evidence of disease (mean 3.2 years). Therefore, patients with higher stage disease were more likely to develop metastatic disease or die with disease than lower stage patients. There was no

**Fig. 5 a** Syncytium of pleomorphic cells with high nuclear to cytoplasmic ratio (400x). **b** Focal areas of squamous differentiation and adjacent tumor necrosis (400x). **c** Pleomorphic tumor cells showing prominent nucleoli within vesicular nuclei (400x). **d** Tumor cell spindling was noted in a few cases (400x)
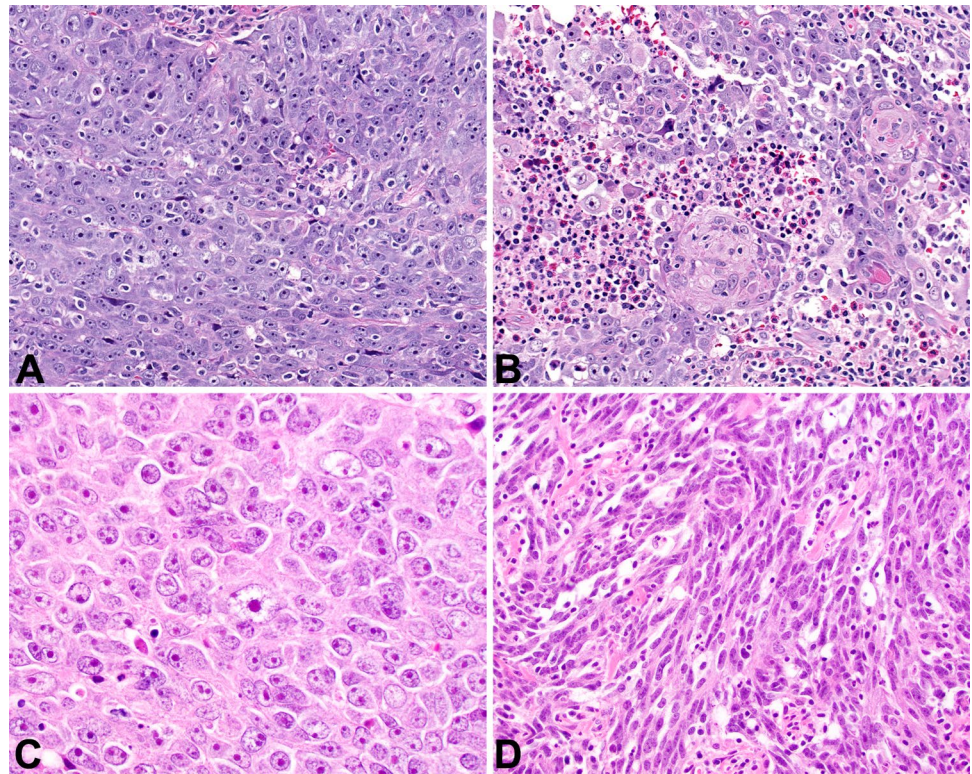


**Fig. 6 a** There is a strong, diffuse, membranous and cytoplasmic reaction with CK5/6 (100x). **b** There is a wispy, lattice-like cytoplasmic reaction with AE1/AE3 (400x). **c** The nuclei of the neoplastic cells are strongly reactive with p63 (400x). **d** A strong, diffuse, nuclear reaction in all of the neoplastic epithelial cells with EBER ISH (200x)
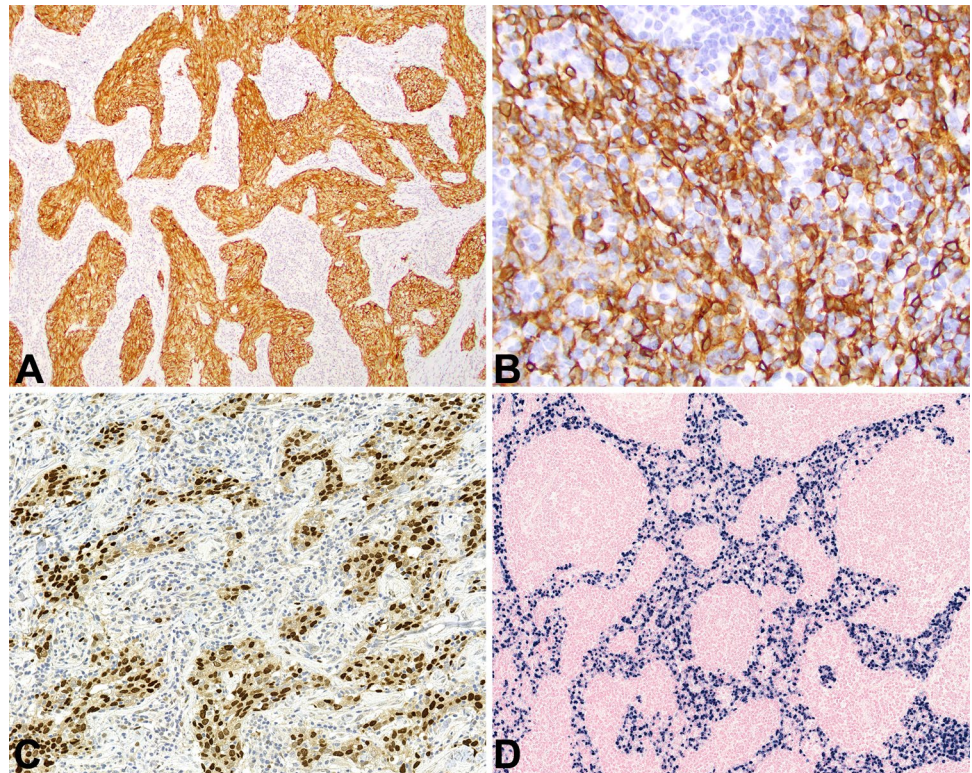


statistically significant survival difference between submandibular gland primaries and parotid gland primaries. There does not appear to be a difference in outcome based on ethnicity: 1 Asian patient had died with disease (4.2 years), and 1 white patient was alive with disease (1.9 years), while all others had no evidence of disease. Similarly, there is no

difference in outcome between females (mean 4.4 years) or males (mean 4.0 years), with one each having disease at last follow-up. All of the 8 EBER-negative patients were without evidence of disease at last follow-up (mean 3.6 years), while 2 of the EBER-positive patients had disease (mean 3.0 years) and 6 patients were without evidence of disease (mean 5.4 years).

Of the patients managed by surgery alone, 1 had died with disease (4.2 years), while the remaining 5 were alive or dead without disease (average 6.3 years). Six patients were managed with surgery and radiation and all were alive without evidence of disease, but only followed for a mean of 1.8 years. Of the 4 patients managed with combination surgery, radiation and chemotherapy, 1 was alive with disease (1.9 years), and the other 3 were alive without evidence of disease (mean 6.3 years).

## Discussion

In the vast majority of LECSG cases, the etiologic role of EBV is well documented, with EBV identified in the neoplastic epithelial cells by in situ hybridization or latent membrane protein (LMP) reactivity [6, 8, 15, 16, 19, 20]. The EBV-association is particularly well developed in patients who are also well known to develop NPC, with remarkably overlapped incidence of the endemic patients: South eastern Chinese, Arctic region natives (Eskimos/Inuits from Alaska, Canada, Greenland), Japanese, northern Africans, and Mongolians [6, 8–15, 21–25]. Whites and blacks make up only a small proportion of patients [17, 18], without a well-documented EBV-association. In this cohort of patients, all Asian patients' tumors were EBV-associated, but neither of the black patients' tumors were EBV-associated, and only 4 of 10 white patients' tumors showed EBV-association. Further, when tested, these EBV-negative cases did not show p16 immunoreactivity. Thus, there is clearly a much more complicated interaction between genetic (ethnic), environmental, geographical, behavioral and viral (EBV) factors in the oncogenic process of LEC [18, 25, 26].

There was no sex predilection in our patients, similar to reported data. In this case series, there is a wide age range at presentation, although when separated by ethnicity, non-endemic patients tend to be older (mean 59.3 years) than endemic patients (mean 44.0 years), a finding similarly reported in the literature for non-endemic patients (median, 62 years) [18, 27–32].

A mass is the usual clinical presentation, with symptoms usually present for about 12 months. Major salivary gland sites are most commonly affected, and account for 93% of the cases in the literature, similar to our results. More than half of the patients in this series had cervical lymph node involvement at the time of presentation, a finding that is higher than reported in the literature (about 15%) [10, 33–36].

LEC shows a histologic appearance that is quite indistinguishable from NPC, non-keratinizing (undifferentiated) type, although the ratio of epithelial to lymphoid component is quite variable cases to case. In this series, 81% (13 of 16) of cases showed a background of lymphoepithelial sialadenitis (LESA). Whether it is a reaction to the tumor or a precursor of the neoplasm, when it is seen adjacent to or within the tumor, it favors a primary lesion over a metastatic tumor [2, 5, 31, 37–41]. None of the patients in this series had laboratory findings supporting Sjögren syndrome. The pattern of either individual cells or islands-sheets of cells, arranged as a syncytium of crowded, large, undifferentiated cells with vesicular to open nuclear chromatin, adjacent to or blended with a lymphoplasmacytic stroma is classical and characteristic [10, 22, 42]. Definitive squamous differentiation may be present, but is usually limited, while a basaloid morphology can be identified [43]. Noncaseating granulomatous inflammation including multinucleated giant cells and even amyloid may rarely be seen [42, 44–46]. A stromal desmoplastic reaction may be focally noted, but is not usually a prominent finding. Tumor cell spindling may be prominent, and when present brings to mind basal cell adenoma/adenocarcinoma and myoepithelial carcinoma [5, 8, 31, 47, 48]. However, none of these other tumors are reactive with nuclear EBER by ISH [8, 9, 25, 28, 47]. While it could go without saying, importantly, no EBER nuclear reaction was identified in the adjacent lymphocytes nor in the epithelial cells of LESA. Even though 8 cases in this series were EBER-negative, the overall histologic pattern and epithelial reactivity was still characteristic of LECSG, and the outcome is identical to the EBER-positive cases. Thus, the diagnosis should still be applied in these cases.

A variety of reactive and neoplastic conditions may be brought to mind when evaluating this type of "undifferentiated" lesion, but a lymphoepithelial lesion, reactive tumor associated lymphoid proliferation (TALP), lymphadenoma, and Warthin tumor generally lack a rapid clinical onset, any significant atypia, are not destructive, maintain a lobular or even distribution of epithelial elements, an oncocytically altered epithelium or have a papillary architecture, and are negative with EBER [49–53]. Generally, lymphomas of the salivary gland are either extranodal marginal zone B-cell lymphomas (which are not EBV-associated) or diffuse large B-cell lymphomas, some of which may be EBV-associated [54–58]. In lymphomas, the lack of any epithelial markers will aid in diagnosis, whether EBV-associated or not [55, 58–60]. Exclusion of a nasopharyngeal primary has already been stated, but clinical, endoscopic, imaging and even biopsy results from the nasopharynx must be incorporated to exclude this possibility. Rarely, a lymphoepithelial pattern

may be seen in HPV-associated oropharyngeal squamous cell carcinoma, and salivary gland metastasis may be seen. A strong, diffuse, nuclear and cytoplasmic p16 reaction in > 70% of the neoplastic cells and/or ISH for high risk human papillomavirus may be helpful in this setting to confirm an oropharyngeal primary [61–63]. Poorly differentiated squamous cell carcinoma (SCC) may present as metastatic disease to the parotid gland and associated lymph nodes. Most are not a lymphoepithelial pattern, but show well developed keratinization and squamous pearl formation. Skin primaries are not EBER reactive, but would be difficult to separate in EBV-negative LECSG. Just like excluding a nasopharyngeal primary site, careful clinical correlation with known skin or mucosal primary SCC must be achieved. Large cell undifferentiated carcinoma (lacking evidence of glandular, squamous, or neuroendocrine differentiation) has an organoid growth, minimal differentiation, high mitotic rate, and coagulative necrosis, but lacks the lymphoid infiltrate and by definition lacks EBV [10, 64–66]. Thus, in EBV-negative LECSG, the lack of lymphoid infiltrate would help make this distinction, a challenge if reviewing only core needle samples. Metastatic melanoma is non-cohesive, but will be reactive with various melanocytic markers [67–69].

The optimal management of LECSG is complete surgical resection with clear surgical margins followed by adjuvant radiotherapy to the tumor bed and neck. Wider surgical margins may not be beneficial, associated with decreased progression free survival and neck fibrosis [5, 15, 18, 70]. As lymph node metastasis is frequently present, elective neck dissections should be performed when biopsy proven metastases or suspicious imaging findings are documented [10, 15, 23, 25, 71]. While there is a stage-related outcome difference, lymph node status at presentation may not adversely affect prognosis [18]. It seems that combination therapies, including chemotherapy, may yield the best overall patient outcome, as it is well known that LEC is highly radiosensitive with high rates of locoregional tumor control [31]. Similar to the literature, when disseminated disease is documented, there is a strong correlation with death from disease [10, 15, 18, 25, 65, 71–73]. The overall 81% 5-year raw survival [10, 15, 18, 22, 36, 74–76] is quite similar to this cohort of patients, the majority of whom are alive without evidence of disease (mean, 4.3 years).

## Conclusions

LECSG irrespective of race or ethnicity, may express EBER, but a significant proportion of non-endemic patients may not be EBV-associated. Patients are usually middle aged without a sex bias, presenting with a mass in a major salivary gland site. Concurrent lymphoepithelial lesions may help suggest a primary tumor. Still, it must be emphasized that thorough clinical, endoscopic and imaging studies of the nasopharynx must be completed prior to implementing therapy. The undifferentiated histology associated with a nonneoplastic lymphoplasmacytic cell infiltrate is quite classical for LEC, with EBER easily identified by ISH when tumors are EBV-associated. As the tumors are exquisitely radiosensitive, combination multimodality therapy will yield an excellent outcome, whether EBV-associated or not and whether lymph node metastases are present or not.

## Compliance with Ethical Standards

**Conflict of interest** All authors declare that they have no conflict of interest as it relates to this research project.

**Ethical Approval** All procedures performed in this retrospective data analysis involving human participants were in accordance with the ethical standards of the institutional review board (IRB #5968), which did not require informed consent. The opinions or assertions contained herein are the private views of the authors and are not to be construed as official or as reflecting the views of Southern California Permanente Medical Group.

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